Natural products. Antitubulin effect of congeners of *N*-acetylcolchinyl methyl ether: synthesis of optically active 5-acetamidodeaminocolchinyl methyl ether and of demethoxy analogues of deaminocolchinyl methyl ether[1]

O. Boyé and A. Brossi[2]

Laboratory of Structural Biology, Natural Products Section, NIDDK, National Institutes of Health, Bethesda, MD 20892, U.S.A.

H. J. C. Yeh

Laboratory of Analytical Chemistry, NIDDK, National Institutes of Health, Bethesda, MD 20892 U.S.A.

E. Hamel

Laboratory of Molecular Pharmacology, DTP, DCT, NCI, National Institutes of Health, Bethesda, MD 20892, U.S.A.

and

B. Wegrzynski and V. Toome

Research Division, Hoffmann-La Roche Inc., Nutley, NJ 07110, U.S.A.

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This paper is dedicated to Dr. Zdenek (Denny) Valenta on the occasion of his 65th birthday

O. Boyé, A. Brossi, H. J. C. Yeh, E. Hamel, B. Wegrzynski, and V. Toome. Can. J. Chem. **70**, 1237 (1992).

Trimethoxy-substituted dihydrodibenzocycloheptenes **4–7**, required for a structure–activity study measuring the inhibition of tubulin polymerization in vitro, were synthesized by four different routes: (1) Synthesis of **4** was achieved from 2,3-dimethoxybenzaldehyde via biphenyl aldehyde **17**, chain lengthening to propionic acid **20**, acid-catalyzed cyclization toward ketone **21**, and removal of the carbonyl group. (2) Compound **5** was obtained by eliminating the sterically most hindered methoxy group in **25** or **26** by metal reduction in alcohol. (3) Compound **6** was prepared from biphenyl aldehyde **34** obtained by Grignard reaction on oxazoline **32**. (4) Compound **7** was obtained by reductive deoxygenation of the tetrazolyl ether derivative of *N*-acetylcolchinol **41**. The key role of the aromatic oxygen atoms in colchicine and allo congeners as points of interaction with the colchicine binding site on tubulin was demonstrated by the lack of inhibitory activity of compounds **4–7**. Optically active 5-acetamide **8***a*,*b* isomers of *N*-acetylcolchinyl methyl ether **2** were obtained after chemical resolution of amine **47**. The absolute configuration of the optical isomers **47***a*,*b* and **8***a*,*b* was determined by ^{1}H NMR and CD measurements. These compounds were found inactive as inhibitors of tubulin polymerization.

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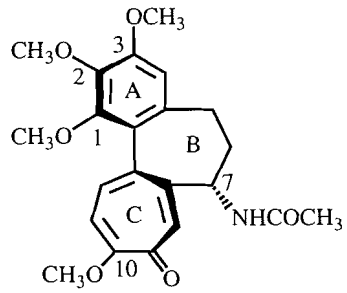
Les triméthoxy-dihydrodibenzocycloheptènes **4–7** ont été synthetisés selon quatre voies différentes dans le cadre d'une étude de relation structure–activité concernant l'inhibition de polymérisation de la tubuline in vitro : (1) la synthèse du composé **4** a été effectuée à partir du 2,3-diméthoxybenzaldéhyde via l'intermédiaire aldéhydique **17** suivi d'une extension de chaîne vers l'acide propionique **20**, donnant, après cyclization, la cétone **21** dont la fonction carbonyle a finalement été réduite. (2) Le composé **5** a été obtenu par élimination du groupement méthoxy encombré de l'alcool **25** ou de l'oxime **26** par réduction métallique. (3) Le composé **6** a été synthétisé à partir de l'aldéhyde biphénylique **34**, obtenu par une réaction de Grignard sur l'oxazoline **32** selon la méthode de Meyer. (4) Le composé **7** provient de la déoxygénation réductive de l'éther de tétrazolyle du *N*-acétylcolchinol **41**. Le rôle clé des atomes d'oxygène aromatiques de la colchicine et des dérivés de type «allo», en tant que points d'interaction avec leur site de fixation sur la tubuline, a été demontré par l'absence de propriétés inhibitrices des composés **4–7**. Les acétamides **8***a*,*b* isomères en position 5 du *N*-acétylcolchinyl méthyl éther **2** ont été obtenues après résolution chimique de l'amine **47**. La configuration absolue des isomères optiques **47***a*,*b* et **8***a*,*b* a été determinée par des mesures de RMN et de dichroïsme circulaire. Ces composés se sont révélés inactifs en tant qu'inhibiteurs de polymérisation de la tubuline.

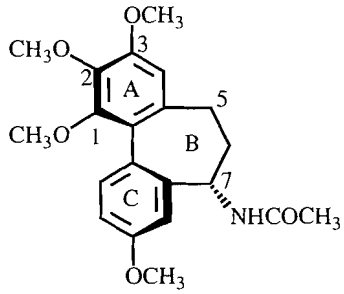
Mapping and full characterization of the colchicine binding site on tubulin remains a challenging and multifaceted research project (1, 2). Modification of natural (−)-(a*S*, 7*S*) colchicine **1** or the parent compound *N*-acetylcolchinol methyl ether **2** offers a possibility to gain valuable information on how these molecules bind to tubulin and inhibit its polymerization. Phenolic congeners of colchicine **1**, especially 1-demethylcolchicine, were found to be less potent than colchicine itself (1–4) as inhibitors of tubulin polymerization, with activity partially restored on esterification (5, 6). After the finding of the high potency of 6,7-dihydro-1,2,3,9-tetramethoxy-5*H*-dibenzo[*a*,*c*]cycloheptene (DBCH) **3** (7*a*), the systematic synthesis of its demethoxy derivatives **4–7** was undertaken in order to investigate the contribution of each aromatic oxygen atom in the binding process. The acetamido group in **1** and **2** is not required for binding to tubulin, as indicated by the high activity of compound **3** (7*a*). The investigation included a synthesis of the optically active amides **8***a*,*b*, with the acetamido group at C(5). Determination of their absolute configurations, a primary factor in tubulin binding ability, was made by ^{1}H NMR and CD.

[1]The results of this investigation were presented by O. Boyé at a poster session of the 200th meeting of the American Chemical Society in Washington, D.C., August 26–31, 1990 (Division of Medicinal Chemistry; Abstr. 68).

[2]Author to whom correspondence may be addressed.



1 (a*S*, 7*S*)



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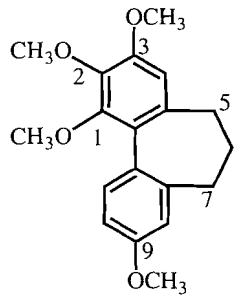

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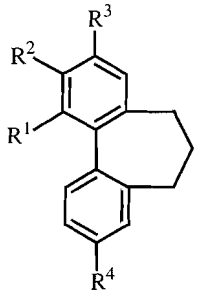
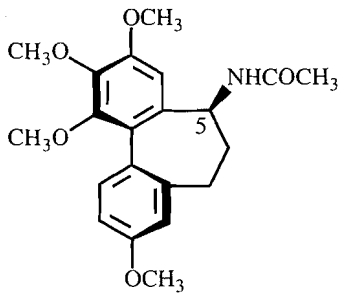
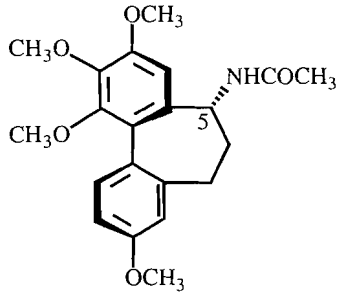


4 $R^1 = R^2 = R^4 = OCH_3$, $R^3 = H$
5 $R^1 = R^3 = R^4 = OCH_3$, $R^2 = H$
6 $R^2 = R^3 = R^4 = OCH_3$, $R^1 = H$
7 $R^1 = R^2 = R^3 = OCH_3$, $R^4 = H$



8A (a*R*, 5*S*)



8B (a*S*, 5*R*)

Chemistry

DBCH 4 from 2,3-dimethoxybenzaldehyde (Scheme 1)

The synthesis of **4** followed a route used earlier in the synthesis of **3** (7*a*, *b*) which started from 2,3,4-trimethoxybenzaldehyde and gave ketone **24** as an intermediate. Azalactone **9**, prepared from 2,3-dimethoxybenzaldehyde and *N*-acetyl glycine, was hydrolyzed to give pyruvic acid **10***a* and acetylated enamine **10***b* as a by-product. The 16-step synthesis of **4** was handicapped by the relatively low yield encountered in the preparation of keto-ester **13** from pyruvic acid **10***a* via Robinson annelation with methyl vinyl ketone (8). The cyclization of acid **20** to ketone **21** in $(CF_3CO)_2O/CF_3COOH$ solution was greatly improved in comparison to previous work (7*a*) by conducting the reaction at low temperature.

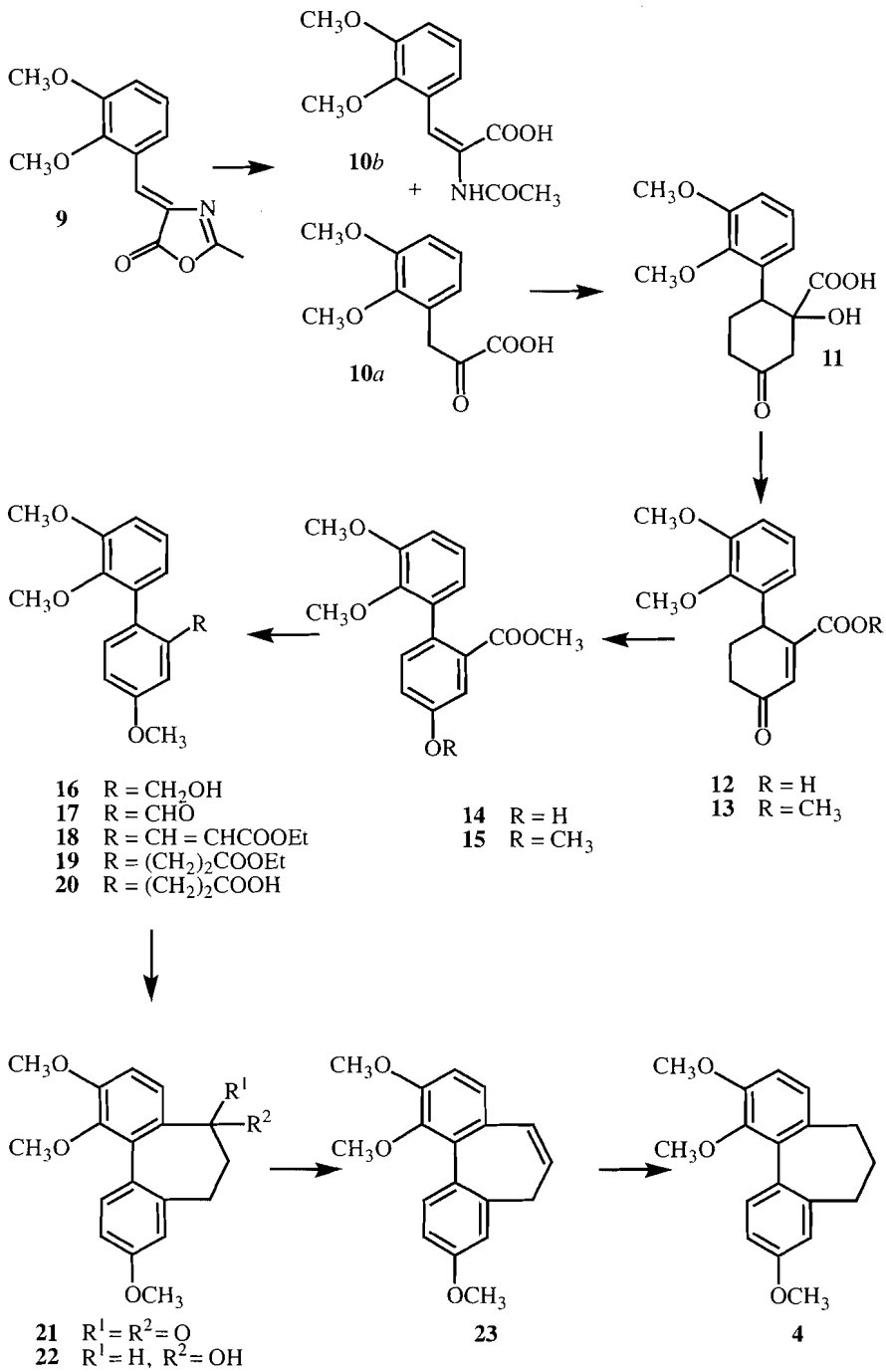
DBCH 5 by sodium–isopropanol reduction (Scheme 2)

Reductive removal of the hindered methoxy group in alcohol **26**, obtained by reduction of ketone **24** (7*a*, *b*), was accomplished with sodium in refluxing isopropanol (12, 13) to afford DBCH **5**. This reaction is reminiscent of methoxy group eliminations observed in the aporphine alkaloid series with sodium in liquid ammonia (18, 19). DBCH **5** could also be obtained starting with oxime **25**, which, treated in the same manner as **26**, was demethoxylated and reduced in a one-pot procedure. Exhaustive methylation of amine **27** afforded quaternary salt **28***b*, which underwent Hofmann elimination to olefin **29**. Reduction of the latter afforded **5**. This material was identical with that directly obtained from **26** on treatment with sodium in isopropanol.

DBCH 6 by Meyers' biphenyl synthesis (Scheme 3)

The synthesis of **6** was tailored after Meyers' efficient synthesis of biphenyl aldehydes from phenyloxazolines with Grignard reagents (14–16).

Reaction of Grignard **31**, prepared from 5-bromoveratrole, with oxazoline **32** (obtained from 2,5-dimethoxybenzoic acid (14–16)) afforded oxazoline **33**. Deprotection of **33** was accomplished by quaternization with methyltriflate, reduction of the quaternary salt with sodium borohydride, and hydrolysis with oxalic acid to give aldehyde **34** (16). Conversion of aldlehyde **34** into ketone **38**, olefin **40**, and DBCH **6** followed the route used for the preparation of **3** and **4**.



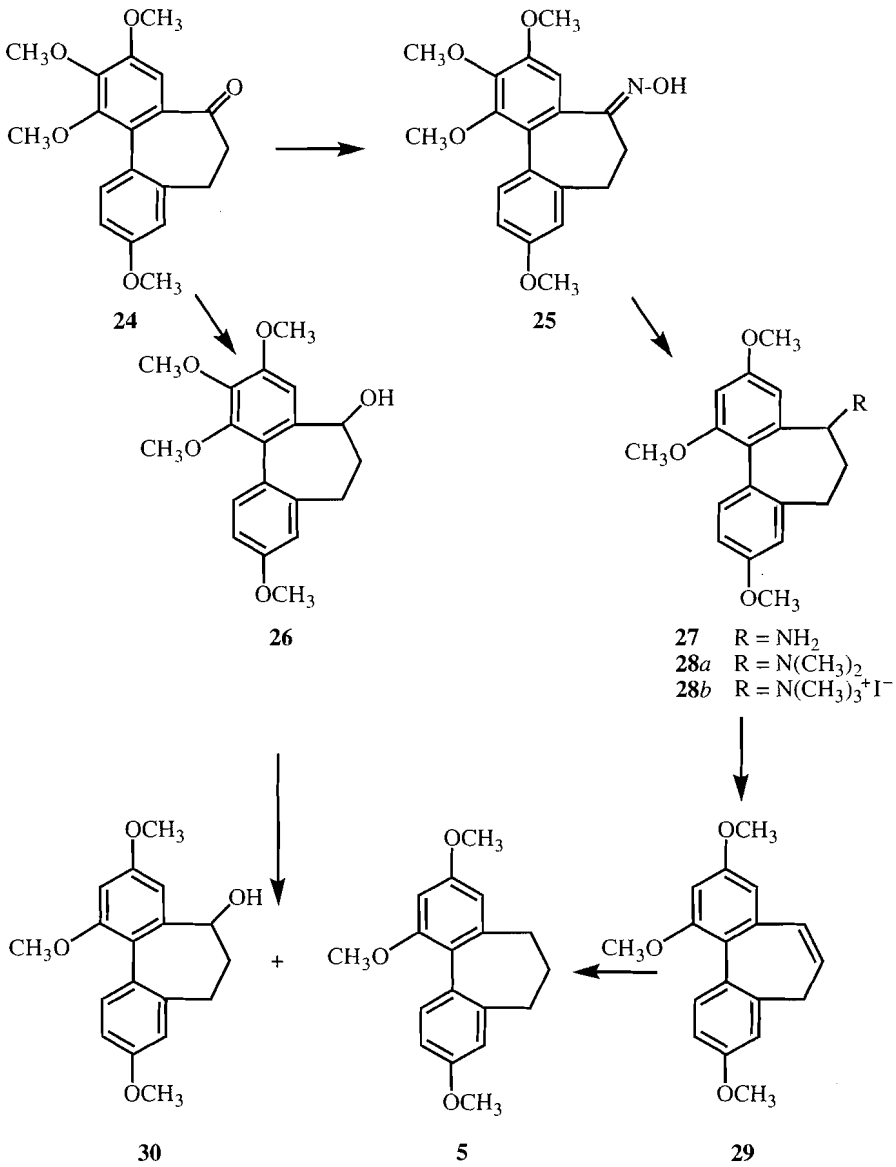
SCHEME 1

DBCH 7 from N-*acetylcolchinol* ***41*** *(Scheme 4)*

N-Acetylcolchinol, prepared from colchicine **1** by a published procedure (17), was deoxygenated by catalytic reduction of its phenyltetrazolyl ether **42** over Pd/C catalyst in acetic acid (20, 21), affording amide **43**. The latter on acid hydrolysis gave amine **44**, which after quarternization with methyl iodide and Hofmann degradation afforded olefin **46** and DBCH **7** on further reduction.

Synthesis of optically active 5-acetamidodeaminocolchinyl methyl ethers **8***a*,b *(Scheme 5)*

Oxime **25** was also used to prepare the optically active isomers **8***a*,*b* (Scheme 5). Reduction of oxime **25** with hydrazine in the presence of Raney nickel catalyst afforded the racemic amine **47**, which was resolved with (+)- and (−)-dibenzoyltartaric acids in isopropanol to afford the optically active amines **47***a*,*b* after recrystallization from MeOH. Further acetylation gave the optically active amides **8***a*,*b*. The optical purity of the amines was measured by HPLC analysis of their urea derivatives **48***a*,*b*. The absolute configuration of compounds **47***a*,*b* and **8***a*,*b* was established by ^{1}H NMR spectroscopy and CD analysis. We have previously shown that natural (−)-7*S*-colchicine **1** and derived allo congeners exhibit negative Cotton effects at 260 nm (9, 10). This optical behavior results from the presence of the noncoplanar biaryl system. Ring C is twisted out of the plane

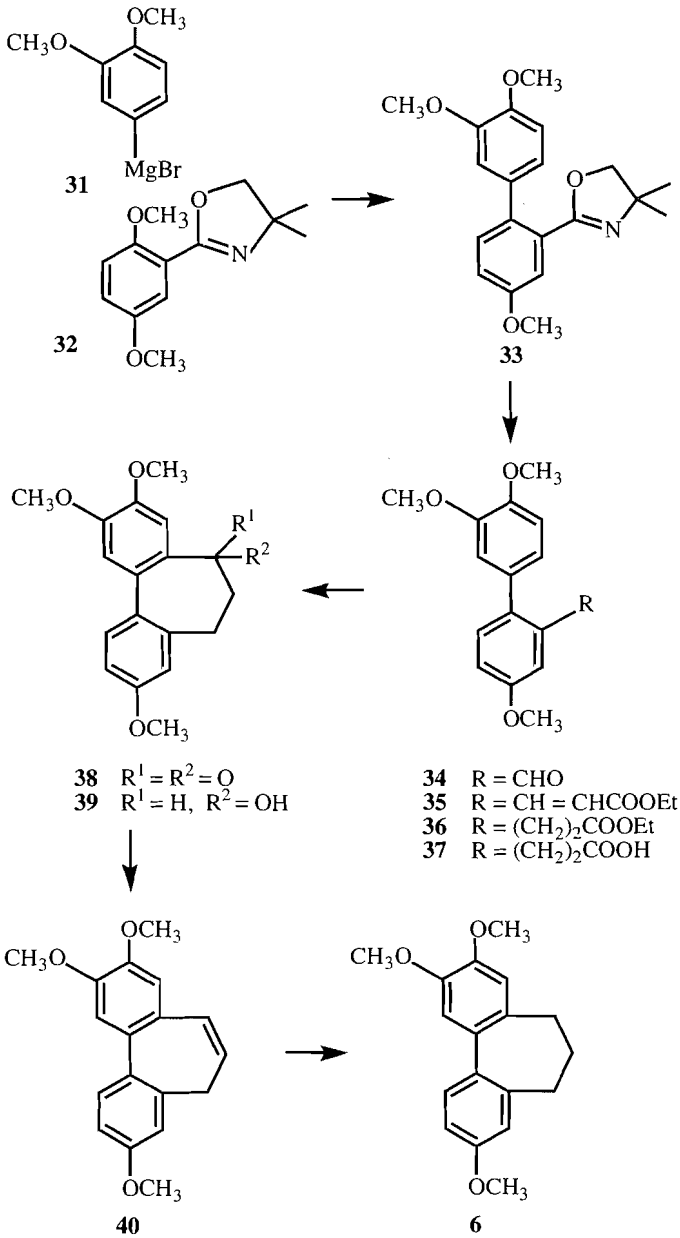


SCHEME 2

formed by ring A in a counterclockwise arrangement with a dihedral angle between the planes of ca. 53° (8). This gives an a*S* assignment to natural (−)-7*S*-colchicine, after consideration of the order of the *ortho–ortho'* substituents of the central bond, according to the chirality rules of Prelog and Helmchen (11). Counterclockwise arrangement of the biaryl systems is manifested by all the biologically active colchicinoids and their allo congeners and is considered to be an important molecular feature in their ability to bind to tubulin. Unnatural (+)-7*R*-colchicine, which has the biaryl system arranged in a clockwise fashion and has a positive Cotton effect at 260 nm, does not bind to tubulin.

Conformational equilibria and absolute configurations of 5-aminodeaminocolchinyl methyl ethers **47**a,b *and derived acetamides* **8**a,b

The optically active amines **47***a,b* and the derived acetamides **8***a,b* are in a solvent-dependent conformational equilibrium (Scheme 5). The absolute configurations of **47***a* and **8***a* were established as follows: the observed negative Cotton effect at 260 nm in ethanol (Fig. 1*a*) for **47***a* and **8***a* suggests that the phenyl rings in these compounds are arranged in a counterclockwise fashion, as in natural (−)-(a*S*,7*S*)-colchicine **1**. Despite the identical helicity of the biaryl system the configuration of **47***a* and **8***a* is a*R* due to the change occurring in the priority of the *ortho–ortho'* substituents as compared to (−)-colchicine (11). In conjunction with this finding, the 5*S* absolute configuration of these molecules was then derived by measuring vicinal proton coupling between H-C(5) and $H_{a,b}$-C(6) (Table 1). The dihedral angles between these protons were evaluated using the Karplus rule (23, 24). By examining the Dreiding model with the biphenyl system arranged in a counterclockwise configuration, one can conclude that H-C(5) in both compounds is axially oriented with the amino or acetamido groups in an equatorial position. This leads to a 5*S* absolute configuration for **47***a* and **8***a*. The solvent dependency of the conformational equilibrium is different for **47***a* and **8***a*. Whereas the ^{1}H NMR proton signal for H-(5) in amine **47***a* does not change significantly on switching solvents from CD_3OD to $CDCl_3$ and the negative Cotton effect at 260 nm is still sub-



SCHEME 3

stantial, these situations are drastically different in the case of acetamide **8***a*. In $CDCl_3$, proton H-C(5) for **8***a* gives two ^1H NMR signals of nearly equivalent intensity, indicating a displacement of the conformational equilibrium toward the a*S* isomer, with the biphenyl system arranged in a clockwise fashion and with the acetamido group axially oriented. The existence of two isomers cannot be explained by a simple *cis–trans* rotameric arrangement of the amide group. This is shown by the optical behavior of **8***a*. The equilibration between a*R*- and a*S*-**8***a* conformers is demonstrated by the drastic decrease in the absorption at 260 nm in the CD spectra in $CHCl_3$ compared to the one displayed in ethanol (Fig. 1*a*, *b*). The specific optical rotation of **8***a* remains constant on standing in methanol and changes very little after several days in chloroform solution. This clearly indicates that the proportion of **8***a* (a*R*,5*S*) and (a*S*,5*S*) isomers present in solution is rapidly established and strongly influenced by the solvent. The optical isomer **8***b*, which was also analyzed, showed similar optical behavior.

Biological evaluation

Method (25)

The compounds were tested as potential inhibitors of the polymerization of purified bovine brain tubulin in vitro. Reaction components were 1.0 mg/mL (10 μM) tubulin, 1.0 M monosodium glutamate (inducer of polymerization), 1.0 mM $MgCl_2$, and 0.4 mM GTP (an essential cofactor for polymerization). All compounds were dissolved in dimethyl sulfoxide (with a final solvent concentration of 4%(v/v), which did not affect the polymerization reaction). All components except GTP were preincubated at 37°C for 15 min to permit the interaction of slow binding agents with tubulin. Reaction mixtures were chilled on ice and after addition of GTP were transferred to thermostated cuvettes held at 0°C in a recording spectrophotometer. Polymerization was initiated by a 75-s temperature jump to 37°C, and the reaction was followed turbidimetrically at 350 nm. For each compound an IC_{50} value was obtained in at least three independent experiments. The IC_{50} value was defined as the drug concentration that inhibits the extent of polymerization by 50% after a 20-min incubation. Values over 50 μM represent negligible activity in this assay, while the lowest IC_{50} value yet obtained has been 1.2 μM (i.e., 50% inhibition of polymerization when at most 12% of the tubulin in the reaction mixture has bound the inhibitor).

Results and discussion

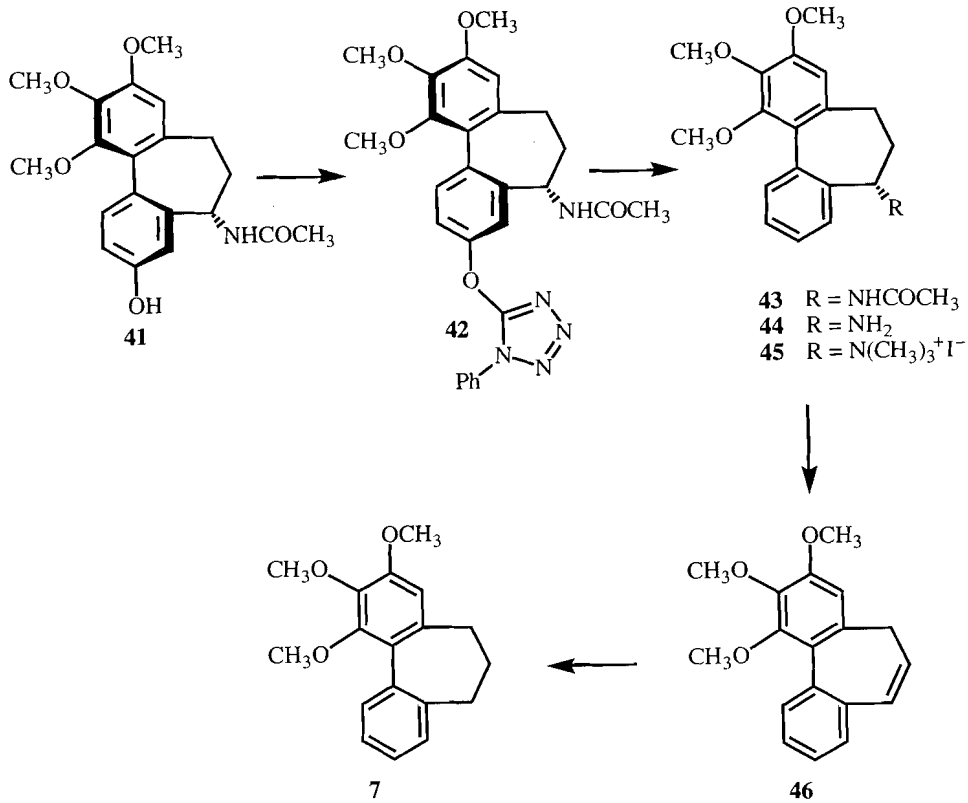
Of the newly prepared compounds, only **5**, **29**, and **43** retained some activity as inhibitors of tubulin polymerization when compared with data obtained for colchicine **1** and *N*-acetylcolchinol methyl ether **2** (Table 2). *This marks dihydrodibenzo[*a,c*]cycloheptene **3** as the simplest tricyclic structure of this series that shows a high antitubulin activity.*

Any replacement of methoxy groups by hydrogen in **3** results in a substantial loss of activity, which is much greater than the loss observed in going from colchicine **1** to demethylated congeners (Table 2). This clearly demonstrates the importance of oxygen atoms at positions C(1), C(3), and C(9) (C(10) in colchicine) as major points of electrostatic interaction with the binding site while the oxygen in C(2) is slightly less important. The substituent at C(1) is also particularly critical because it affects the a*R*–a*S* equilibrium through steric hindrance with H-C(11). Switching the acetamido group from C(7) as in **2** to C(5), despite a proper counterclockwise absolute configuration for **8***a*, afforded inactive compounds **8***a*,*b*. Even an amino group at position C(5), as in **47***a*, resulted in complete loss of activity. This suggests that substitution at this position interferes with the tubulin binding process.

Experimental

General

TLC: silica gel GHLF plates from Analtech; visualization with UV light, I_2, Dragendorff's solution. Flash chromatography: silica gel 60 (Fluka), 230–400 mesh, 60 Å. Melting point (uncorrected): Fisher–Johns melting point apparatus. IR spectra: Beckman IR 4230. ^1H NMR spectra: Varian XL 300 (300 MHz). CIMS:



SCHEME 4

Finingan 1015 D; EIMS: VG 7070 F. GC: Hewlett Packard 5890A, column HP-1 (cross linked methyl silicone gum) 25 m × 0.32 mm. HPLC: Shimadzu LC-6A, column Alltech 250 mm, i.d. 4–6 mm fitting B. Optical rotation: Perkin–Elmer polarimeter 241MC.

Synthesis of DBCH ***4*** *(Scheme 1)*

*3-Methyl-4-[(2,3-dimethoxyphenyl)-methylidene]-5(4*H*)-oxazolone* ***9***

Oxazolone **9** was prepared according to published procedure (*7b*) and recrystallized from toluene as a bright yellow powder (39%): mp 130°C; IR ($CHCl_3$): 3020 (CH_3), 1810, 1770 (O-C=O), 1660 (C=NH), 1260 (Ph-O-CH_3) cm^{-1}; ^1H NMR ($CDCl_3$) δ: 2.40 (s, CH_3), 3.89 (s, CH_3O), 3.90 (s, CH_3), 7.00 (dd, J = 8.1 and 1.3 Hz, 1H, 4′-H), 7.14 (t, J = 8.1 Hz, 1H, 5′-H), 7.65 (s, 1H, Ph-CH=), 8.23 (dd, J = 8 and 1.4 Hz, 1H, 6′-H); CIMS (NH_3) m/z: 248 (MH^+). Anal. calcd. for $C_{13}H_{13}O_4N$ (247.25): C 63.15, H 5.30, N 5.66; found: C 63.06, H 5.33, N 5.60.

3-(2,3-Dimethoxyphenyl)pyruvic acid ***10***

A solution of **9** (50.0 g, 0.2 mol) in aqueous HCl (10%, 90 mL) and dioxane (180 mL) was refluxed for 3 h. After cooling, the solvents were evaporated to give a residue that was dissolved in ethyl acetate and washed with H_2O. The acid was extracted from the organic layer with concentrated ammonium hydroxide. The aqueous layer was washed with ethyl acetate, then acidified with concentrated HCl. The acid was then extracted with ethyl acetate. After washing with H_2O until neutral, and drying (Na_2SO_4), the solvent was evaporated to give 22 g of **10** (yield 49%), which was recrystallized from toluene to give a yellow powder: mp 123–124°C; IR ($CHCl_3$): 3460 (OH), 3000 (CH_3), 1690 (C=O), 1475, 1270 (CH_3O) cm^{-1}; ^1H NMR ($CDCl_3$) δ: 3.88 (s, CH_3O), 3.9 (s, CH_3O), 6.92 (d, J = 8.1 Hz, 1H, 4′-H), 6.94 (s, 1H, Ph-CH=), 7.12 (t, J = 8 Hz, 1H, 5′-H), 7.33 (d, J = 7.9 Hz, 1H, 6′-H); CIMS (NH_3) m/z: 242 ($MH^+ + NH_3$), 224 (M^+). Anal. calcd. for $C_{11}H_{12}O_5$(224.21): C 58.93, H 5.39; found: C 58.68, H 5.43.

1-Hydroxy-5-oxo-2-(2,3-dimethoxyphenyl)-1-cyclohexanecarboxylic acid ***11***

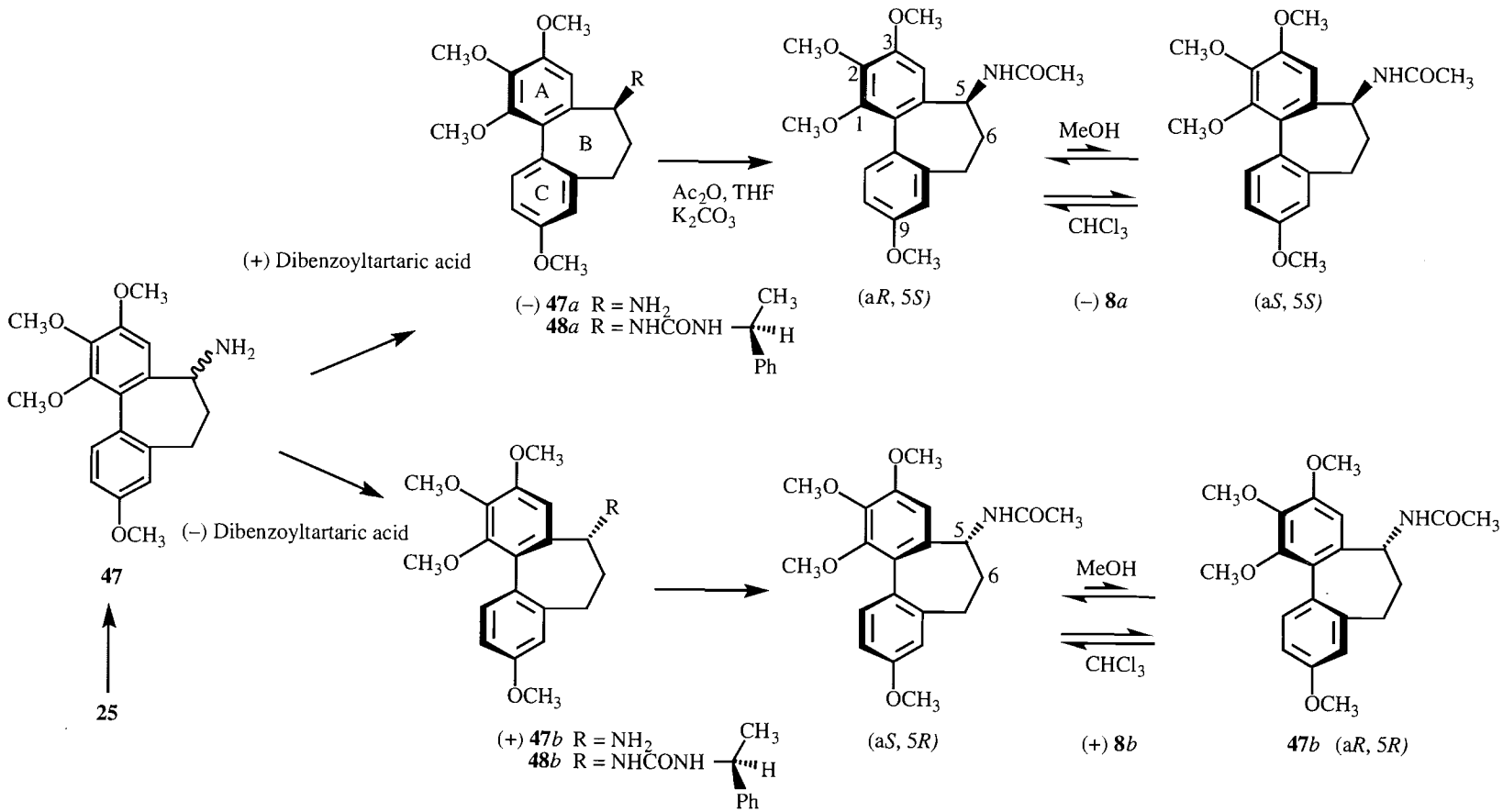
Acid **11** was prepared by published procedure (*7b*) as a crude mixture (57 g, 81%); a sample of the product (4 g) was flash chromatographed for analysis (SiO_2, $CHCl_3$–MeOH–CH_3COOH 9.25:0.5:0.25), giving **11** as a translucide oil (0.5 g, 10%): ^1H NMR ($CDCl_3$) δ: 1.45–2.26 (m, 4H, CH_2), 2.35 (d, J = 15 Hz, 1H, $CH_2C(OH)COOH$), 2.72 (d, J = 14.9 Hz, 1H, $CH_2C(OH)COOH$), 3.42 (dd, J = 12.9 and 3.7 Hz, 1H, CH), 3.58 (s, 3H, CH_3O), 3.62 (s, 3H, CH_3O), 5.68 (s, 1H, OH), 6.57 (d, J = 8.1 Hz, 1H, 4′-H), 6.63 (d, J = 8 Hz, 1H, 6′-H), 6.74 (t, J = 7.9 Hz, 1H, 5′-H). Recrystallization from ethyl acetate gave white crystals; mp 209–212°C (dec.); IR (film): 3460 (OH), 2930, 1720 (C=O), 1655–1620 (C=O), 1470 cm^{-1}; CIMS (NH_3) m/z: 329 ($MH^+ + 2NH_3$), 312 ($MH^+ + NH_3$), 295 (MH^+), 276 ($MH^+ - H_2O$).

3-Oxo-6-(2,3-dimethoxyphenyl)-1-cyclohexenecarboxylic acid ***12***

Acid **12** was prepared from crude compound **11** by published procedure (*7b*), obtained as a yellow oil (98%, crude), and used without further purification in the preparation of ester **13**; CIMS (NH_3) m/z: 294 ($MH^+ + NH_3$), 276 (M^+), 259 ($MH^+ - OH$).

Mixture of methyl 3-oxo-6(2,3-dimethoxyphenyl)-1-cyclohexene-1-carboxylate and methyl 5-oxo-2-(2,3-dimethoxyphenyl)-1-cyclohexene-1-carboxylate ***13***

K_2CO_3 (40.0 g, 0.29 mol) and MeI (25 mL, 0.4 mol) were added to a solution of acid **12** (44 g, crude, 0.15 mol) in anhydrous THF (250 mL). The mixture was refluxed for 4 h under N_2. After cooling, K_2CO_3 was removed by filtration and washed with Et_2O. The filtrate was evaporated to give a residue that was dissolved in ethyl acetate. The organic layer was washed with brine and dried (Na_2SO_4) to give, after evaporation, 42 g of a brown oil. The



SCHEME 5

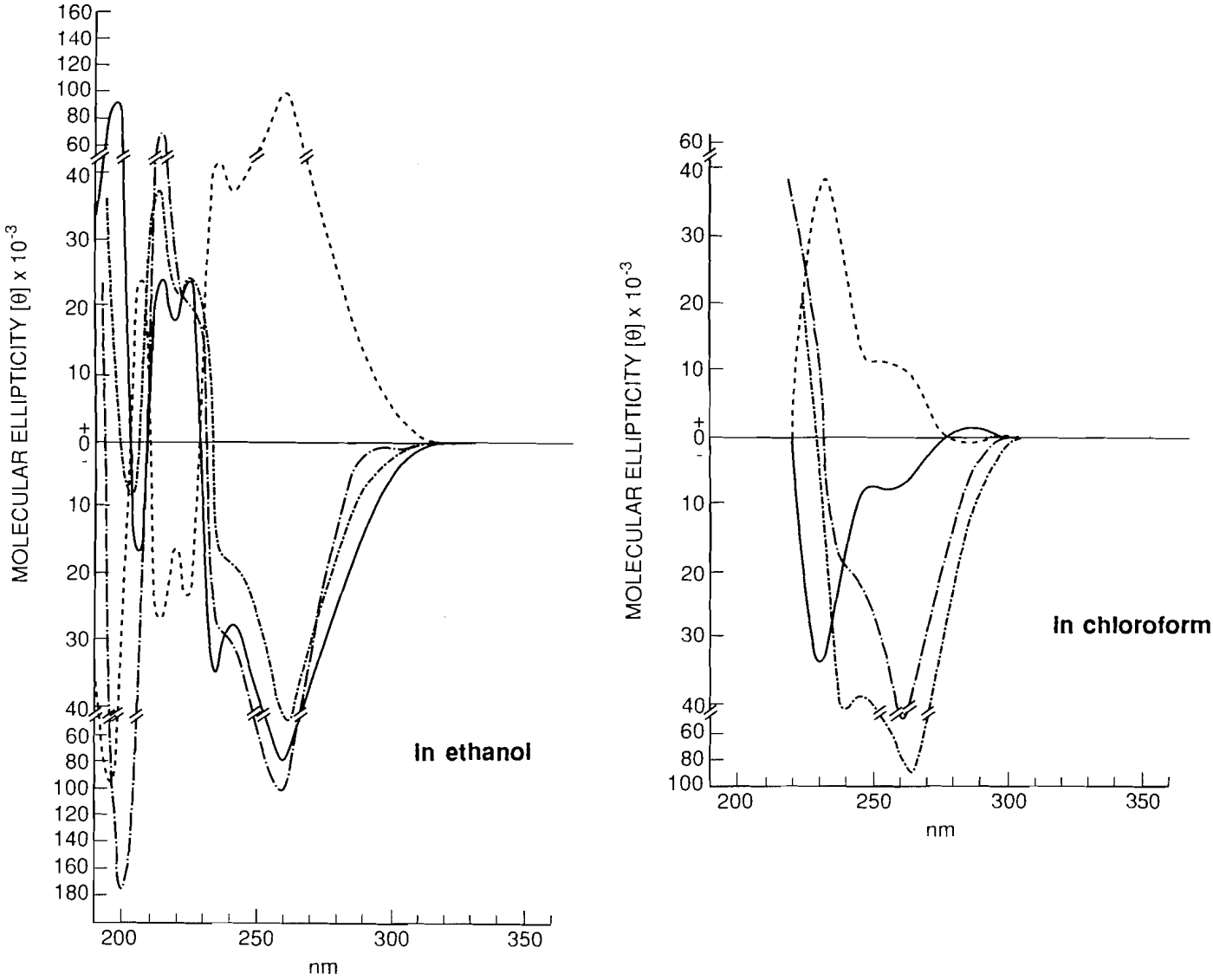


FIG. 1. CD spectra of *N*-acetylcolchinyl methyl ether **2** and its analogs **8***a*,*b* and **47***a*. (——) **8***a*; (- - - -) **8***b*; (—·—) *N*-acetylcolchinyl methyl ether **2**; (—·—·—·) **47***a*.

TABLE 1. Chemical shifts (ppm) of proton H(5) and its vicinal coupling constants (Hz), $J_{5,6a}$ and $J_{5,6b}$, in (*S*)-5-acetamidodeaminocolchinyl methyl ether **8***a* and (*S*)-5-aminodeaminocolchinyl methyl ether **47***a* in different solvents

	a*R* Conformation			a*S* Conformation			
	δH(5) ppm	$J_{5,6a}$ Hz	$J_{5,6b}$ Hz	δH(5) ppm	$J_{5,6a}$ Hz	$J_{5,6b}$ Hz	%a*R*
(*S*)-5-Acetamidodeaminocolchinyl methyl ether **8***a*							
Methanol-d_4	4.44	12.4	6.6	Not determined			~93
Acetone-d_6	4.62	12.2	6.1	Not determined			~92
Chloroform-*d*	4.59	12.2	6.2	5.00	~0	6.2	~46
(*S*)-5-Aminodeaminocolchinyl methyl ether, HCl salt **47***a*							
Methanol-d_4	3.90	11.8	6.3	Not determined			~95

product was chromatographed (SiO_2, eluent ethyl acetate – hexanes 1:4, then 3:7), giving a yellow oil that was crystallized from *i*PrOH – petroleum ether as pale yellow crystals (21%): mp 77–78°C; IR ($CHCl_3$): 3010, 2960 (CH_3), 1730 (C=O), 1685 (C=O), 1590 (Ph), 1480 (-CH_2-), 1290–1200 (Ph-O-CH_3) cm^{-1}; ^1H NMR ($CDCl_3$) δ: 1.63–2.04 (m, 2H, CH_2), 2.23–2.4 (m, 4H, CH_2), 3.62 (s, 3H, CH_3O), 3.8 (s, 3H, CH_3O), 3.87 (s, 3H, CH_3O), 4.52 (br t, *J* = 4.3 Hz, 1H, Ph-CH), 6.47 (dd, *J* = 7.6 and 1.4 Hz, 1H, 4′-H), 6.77 (dd, *J* = 8.2 and 1.4 Hz, 1H, 6′-H), 6.85 (s, 1H, COCH=), 6.88 (t, *J* = 8.0 Hz, 1H, 5′-H); CIMS (NH_3) *m*/*z*: 308($MH^+ + NH_3$), 291 (MH^+), 259 ($M^+ - OCH_3$). Anal. calcd. for $C_{16}H_{18}O_5$ (290.3): C 66.19, H 6.25; found: C 66.10, H 6.27.

Methyl 4-hydroxy-2′,3′-dimethoxy-1,1′-biphenyl-2-carboxylate ***14***

Ethyl ester **13** (2.0 g, 7.2 mmol) was pulverized and thoroughly mixed with Pd black (1.0 g, 9.4 mmol). This powder was heated to 200°C in a Kugelrohr apparatus under moderate vacuum (20 Torr; 1 Torr = 133.3 Pa). After 15 min, high vacuum (0.1 Torr) was applied and the product was distilled for 1 h to give a colorless oil (1.6 g). The residue remaining in the round-bottom flask was dissolved in EtO_2 and the Pd removed by filtration through

TABLE 2. Inhibitory effects of colchicine analogs on tubulin polymerization

Agent	IC_{50} (μM) (±S.D.)
Colchicine	2.4 ± 0.08
1-Demethylcolchicine	6.8 ± 0.5
2-Demethylcolchicine	3.7 ± 0.3
3-Demethylcolchicine	2.9 ± 0.5
Deacetylcolchicine	3.3 ± 0.4
Deacetamidocolchicine	2.6 ± 0.3
2	1.5 ± 0.2
3	1.9 ± 0.3
4	>50
5	23 ± 6
6	>50
7	>50
23	>50
29	9.4 ± 1
40	>50
43	15 ± 2
46	>50
8*a*	>50
8*b*	>50
47*a*	>50

Celite. The product was then chromatographed (SiO_2, ethyl acetate – hexanes 3:7) to give 200 mg more of oil. Total product 1.8 g (91%); IR ($CHCl_3$): 3600–3100 (OH), 2940 (CH_3), 1720 (C=O), 1600, 1570 (Ph), 1470, 1430, 900 cm^{-1}; CIMS (NH_3) *m/z*: 289 (MH^+), 288 (M^+), 257 ($M^+ - OCH_3$).

Methyl 2′,3′,4′-trimethoxy-1,1′-biphenyl-2-carboxylate ***15***

Carboxylate **15** was prepared by published procedure (*7b*) as a pale yellow oil (69%): IR: $CHCl_3$): 3000, 2940, 2815 (CH_3), 1720 (C=O), 1605, 1580 (Ph), 1465, 1300–1200 (CH_3-O-) cm^{-1}; ^1H NMR ($CDCl_3$) δ: 3.47 (s, 3H, CH_3O), 3.66 (s, 3H, CH_3O), 3.87 (s, 3H, CH_3O), 3.88 (s, 3H, CH_3O), 6.81 (dd, *J* = 1.5 and 7.7 Hz, 1H, 4′-H), 6.91 (dd, *J* 1.5 and 8.2 Hz, 1H, 6′-H), 7.07 (dd, *J* = 2.8 and 8.5 Hz, 1H, 5-H), 7.08 (t, *J* = 7.9 Hz, 1H, 5′-H), 7.27 (d, *J* = 8.4 Hz, 1H, 6-H), 7.43 (d, *J* = 2.8 Hz, 1H, 3-H); EIMS *m/z*: 302 (M^+), 271 ($M^+ - CH_3O$).

2′,3′,4′-Trimethoxy-1,1′-biphenyl-2-methanol ***16***

Prepared by published procedure (*7b*) as a colorless oil (82–88%); IR ($CHCl_3$): 3460 (OH), 3000, 2940, 2820 (CH_3), 1600, 1575 (Ph), 1460, 1250 (CH_3-O-) cm^{-1}; ^1H NMR ($CDCl_3$) δ: 3.47 (s, 3H, CH_3O), 3.85 (s, 3H, CH_3O), 3.89 (s,, 3H, CH_3O), 4.34 (br s, 1H, CH_2), 4.38 (br s, 1H, CH_2), 6.77 (d, *J* = 1.4 and 7.6 Hz, 1H, 4′-H), 6.89 (dd, *J* = 2.7 and 8.4 Hz, 1H, 5-H), 6.93 (dd, *J* = 1.4 and 8.2 Hz, 1H, 6′-H), 7.10 (t, *J* = 7.9 Hz, 1H, 5′-H), 7.11 (d, *J* = 2.7 Hz, 1H, 3-H), 7.15 (d, *J* = 8.4 Hz, 1H, 6-H); CIMS (NH_3) *m/z*: 274 (M^+), 257 ($M^+ - OH$).

2′,3′,4-Trimethoxy-1,1′-biphenyl-2-carbaldehyde ***17***

Aldehyde **17** was prepared by published procedure (*7b*) as pale yellow crystals (65%): mp 81–83°C; IR ($CHCl_3$): 3000, 2940, 2840 (CH_3), 1680 (C=O), 1610 (Ph), 1470, 1260 (CH_2-O-) cm^{-1}; ^1H NMR ($CDCl_3$) δ: 3.47 (s, 3H, CH_3O), 3.91 (s, 3H, CH_3O), 3.92 (s, 3H, CH_3O), 6.87 (dd, *J* = 1.4 and 7.6 Hz, 1H, 4′-H), 6.99 (dd, *J* = 1.3 and 8.3 Hz, 1H, 6′-H), 7.14 (t, *J* = 7.9 Hz, 1H, 5′-H), 7.19 (dd, *J* = 2.8 and 8.4 Hz, 1H, 5-H), 7.32 (d, *J* = 8.4 Hz, 1H, 6-H), 7.52 (d, *J* = 2.7 Hz, 1H, 3-H), 9.8 (s, 1H, CHO); CIMS (NH_3) *m/z*: 290 ($MH^+ + NH_3$), 273 (MH^+). Aldehyde **17** was also characterized as its 2,4-dinitrophenylhydrazone derivative, which crystallized in EtOH to give orange crystals; mp 233–234°C; CIMS (NH_3) *m/z*: 453 (MH^+), 270 ($M^+ - (NH - Ph(NO_2)_2)$).

Ethyl 3-(2′,3′,4-trimethoxy-1,1′-biphenyl-2-yl)prop-2-enoate ***18***

Ester **18** was prepared by published procedure (*7a*) (95%) and crystallized from iPr_2O as white crystals: mp 86–87°C; IR ($CHCl_3$): 3000 (CH_3), 1705 (C=O), 1635 (CH=CH), 1605 (Ph), 1470 cm^{-1}; ^1H NMR ($CDCl_3$) δ: 1.09 (t, *J* = 7.2 Hz, 3H, CH_3), 3.34 (s, 3H, CH_3O), 3.70 (s, 3H, CH_3O), 3.73 (s, 3H, CH_3O), 4.00 (q, *J* = 7.2 Hz, 2H, CH_2), 6.18 (d, *J* = 15.9 Hz, 1H, =CHCO), 6.55 (dd, *J* = 1.5 and 7.6 Hz, 4′-H), 6.77 (dd, *J* = 1.5 and 8.3 Hz, 1H, 6′-H), 6.8 (dd, *J* = 2.7 and 8.5 Hz, 1H, 5-H), 6.90 (t, *J* = 7.9 Hz, 1H, 5′-H), 7.04 (d, *J* = 2.6 Hz, 1H, 3-H), 7.08 (d, *J* = 8.5 Hz, 1H, 6-H), 7.38 (d, *J* = 15.9 Hz, 1H, Ph-CH=); CIMS (NH_3): 342 (M^+), 297 (M^+ – OEt). Anal. calcd. for $C_{20}H_{22}O_5$ (342.38): C 70.16, H 6.48; found: C 70.18, H 6.54.

Ethyl 2′,3′,4-trimethoxy-1,1′-biphenyl-2-propionate ***19***

Prepared by published procedure (*7a*) as a colorless oil (99%): IR ($CHCl_3$): 3000, 2940 (CH_3), 1730 (C=O), 1610, 1580, 1470, 1260, 1200 cm^{-1}; ^1H NMR ($CDCl_3$) δ: 1.01 (t, *J* = 7.2 Hz, 3H, CH_3), 2.27 (dt, *J* = 3 and 8.1 Hz, 2H, CH_2COO), 2.64 (t, *J* = 8 Hz, 2H, $PhCH_2$), 3.34 (s, 3H, CH_3O), 3.66 (s, 3H, CH_3O), 3.73 (s, 3H, CH_3O), 3.87 (q, *J* = 7.2 Hz, 2H, $COOCH_2$), 6.58 (dd, *J* = 1.5 and 7.6 Hz, 1H, 4′-H), 6.62 (dd, *J* = 2.7 and 8.3 Hz, 1H, 5-H), 6.67 (d, *J* = 2.7 Hz, 1H, 3-H), 6.75 (dd, *J* = 1.5 and 8.2 Hz, 1H, 6′-H), 6.90 (t, *J* = 7.8 Hz, 1H, 5′-H), 6.94 (d, *J* = 8.1 Hz, 1H, 6-H); CIMS (NH_3) *m/z*: 345 (MH^+), 344 (M^+), 316 (MH^+ – Et), 299 (M^+ – OEt).

2′,3′,4-Trimethoxy-1,1′-biphenyl-2-propionic acid ***20***

Acid **20** was prepared by published procedure (*7a*) as white crystals (100%): mp 147–148°C; IR ($CHCl_3$): 3000, 2940, 2840 (CH_3), 1705 (C=O), 1605, 1575 (Ph), 1500, 1465, 1260, 1200 (CH_3-O-); CIMS (NH_3): 316 (M^+), 299 (M^+ – OH), 271 (M^+ – COOH). Anal. calcd. for $C_{18}H_{20}O_5$ (316.36): C 68.34, H 6.37; found: C 68.16, H 6.39.

*6,7-Dihydro-1,2,9-trimethoxy-5*H*-dibenzo[*a,c*]cyclohepten-5-one* ***21***

Acid **20** (3.0 g, 9.5 mmol) was added to $(CF_3CO)_2O$ (30 mL) and the solution containing undissolved material was cooled to 0–5°C. CF_3COOH (25 mL) was added slowly under argon. The solution was stirred at low temperature and the reaction was followed by GC. After 2 h, additional $(CF_3CO)_2O$ (30 mL) was added. The reaction was stopped after 5 h. The solvent was evaporated, the residue diluted with EtOAc and washed with $NaHCO_3$ solution, brine, and dried (Na_2SO_4). Evaporation of solvent gave 2.7 g of yellow oil, which was chromatographed (SiO_2, ethyl acetate – hexanes 2:3). Ketone **21** was recrystallized from the same solvent system to give 2.62 g of white crystals (92%): mp 127–128°C; IR ($CHCl_3$): 3000, 2940 (CH_3), 1675 (C=O), 1620, 1590 (Ph), 1510, 1480, 1465, 1300–1200 cm^{-1}; ^1H NMR ($CDCl_3$) δ: 2.7–3.04 (br m, 3H, CH_2), 3.06–3.24 (m, 1H, CH_2), 3.49 (s, 3H, CH_3O), 3.84 (s, 3H, CH_3O), 3.94 (s, 3H, CH_3O), 6.81 (d, *J* = 2.4 Hz, 1H, 8-H), 6.84 (dd, *J* = 2.7 and 8.5 Hz, 1H, 10-H), 6.93 (d, *J* = 8.5 Hz, 1H, 3-H), 7.36 (d, *J* = 8.5 Hz, 1H, 4-H), 7.5 (d, *J* = 8.4 Hz, 11-H); CIMS (NH_3) *m/z*: 299 (MH^+). Anal. calcd. for $C_{18}H_{18}O_4$ (298.3): C 72.46, H 6.08; found: C 72.33, H 6.11.

*6,7-Dihydro-1,2,9-trimethoxy-5*H*-dibenzo[*a,c*]cyclohepten-5-ol* ***22***

Prepared by published procedure (*7a*) as a colorless oil (99%): IR ($CHCl_3$): 3600, 3480 (OH), 3020, 2940, 2850 (CH_3), 1610, 1580 (Ph), 1500, 1480, 1460, 1410 (CH_2), 1250–1200 (Ph-O-CH_3), 1100, 1020 cm^{-1}; ^1H NMR ($CDCl_3$) δ: 2.3–2.65 (m, 4H, CH_2), 3.5 (s, 3H, CH_3O), 3.85 (s, 3H, CH_3O), 3.91 (s, 3H, CH_3O), 4.44 (dd, *J* ~ 7 Hz, 1H, *CH*OH), 6.8 (d, *J* = 2.6 Hz, 8-H), 6.84 (dd, *J* = 2.7 and 8.4 Hz, 1H, 10-H), 6.95 (d, *J* = 8.4 Hz, 3-H), 7.34 (d, *J* = 8.4 Hz, 4-H), 7.45 (d, *J* = 8.4 Hz, 11-H); CIMS (NH_3) *m/z*: 283 (MH^+ – H_2O).

*1,2,9-Trimethoxy-7*H*-dibenzo[*a,c*]cycloheptene* ***23***

Alcohol **22** (140 mg, 0.5 mmol) was heated for 3 h at 190–200°C in a Kugelrohr apparatus *in vacuo*. The residue was dissolved in

Et_2O and filtered through celite filtration aid. Evaporation of the filtrate gave an oil, which was chromatographed on SiO_2. Elution with ethyl acetate – hexanes 3:7 gave 30 mg of the dehydrated product and 80 mg of starting material, which was reacted again. Total yield 42.6% of white crystals recrystallized from MeOH: mp 114–115°C, IR ($CHCl_3$): 3000, 2940, 2840 (CH_3), 1610 (Ph), 1500, 1480 (-CH_2-, -CH=CH_2), 1300–1200 (Ph-O-CH_3), 1100 cm^{-1}; ^1H NMR ($CDCl_3$) δ: 2.83 (ddd, J = 2.1, 5.4, and 12.6 Hz, 1H, 7-H), 3.11 (dd, J = 8.2 and 12.8 Hz, 1H, 7-H), 3.5 (s, 3H, CH_3O), 3.84 (s, 3H, CH_3O), 3.94 (s, 3H, CH_3O), 6.14 (m, 1H, 6-H), 6.49 (dd, J = 1.6 and 10.1 Hz, 5-H), 6.75 (d, J = 2.5 Hz, 1H, 8-H), 6.78 (dd, J = 2.7 and 8.5 Hz, 1H, 10-H), 6.93 (d, J = 8.5 Hz, 1H, 3-H), 7.04 (d, J = 8.5 Hz, 1H, 4-H), 7.65 (d, J = 8.4 Hz, 1H, 11-H); CIMS (NH_3) m/z: 283 (MH^+). Anal. calcd. for $C_{18}H_{18}O_3 \cdot H_2O$ (300.34): C 71.98, H 6.71; found: C 72.01, H 6.37.

*6,7-Dihydro-1,2,9-trimethoxy-5*H-*dibenzo*[a,c]*cycloheptene* ***4***

Prepared by published procedure (*7a*) (89%), giving white crystals after recrystallization from methanol: mp 80–81°C; IR ($CHCl_3$): 3020, 2940, 2840 (CH_3), 1610 (Ph), 1505–1450 (-CH_2-), 1300–1200 (Ph-O-CH_3), 1110, 1020, 800–700 cm^{-1}; ^1H NMR ($CDCl_3$) δ: 1.98–2.1 (m, 2H, CH_2), 2.15–2.32 (m, 1H, CH_2), 2.35–2.55 (m, 3H, CH_2), 3.49 (s, 3H, CH_3O), 3.85 (s, 3H, CH_3O), 3.89 (s, 3H, CH_3O), 6.80 (d, J = 2.7 Hz, 1H, 8-H), 6.82 (d, J = 8.3 Hz, 1H, 4-H), 6.85 (dd, J = 2.7 and 8.4 Hz, 1H, 10-H), 6.91 (d, J = 8.2 Hz, 1H, 3-H), 7.47 (d, J = 8.4 Hz, 1H, 11-H); CIMS (NH_3) m/z: 302 ($MH^+ + NH_3$), 285 (MH^+).

Synthesis of DBCH ***5*** *(Scheme 2)*

*6,7-Dihydro-1,2,3,9-tetramethoxy-5*H-*dibenzo*[a,c]*cyclohepten-5-oxime* ***25***

A solution of sodium acetate (150 mg, 1.8 mmol) and hydroxylamine hydrochloride (126 mg, 1.8 mmol) in EtOH (50 mL) was added to **24** (300 mg, 0.9 mmol) in EtOH (100 mL) and refluxed for 12 h. EtOH was evaporated, the residue dissolved in Et_2O and washed with NH_4Cl solution, brine, and dried (Na_2SO_4). Evaporation of the solvent gave a white foam that was recrystallized from ethyl acetate – hexanes 1:4 to give only one conformational isomer of the oxime as brilliant white crystals (96%): mp 176°C; IR ($CHCl_3$): 3600, 3300 (OH), 3000, 2945, (CH_3), 1615 (C=N), 1590 (Ph), 1400, 1360, 1330, 1310, 1250 (Ph-O-CH_3), 1120, 1090 cm^{-1}; ^1H NMR ($CDCl_3$) δ: 2.65–2.69 (m, 1H, CH_2), 2.82–2.92 (m, 2H, CH_2), 3.20–3.32 (m, 1H, CH_2), 3.57 (s, 3H, CH_3O), 3.85 (s, 3H, CH_3O), 3.94 (s, 3H, CH_3O), 3.97 (s, 3H, CH_3O), 6.80 (d, J = 2.7 Hz, 1H, 8-H), 6.82–6.87 (m, 2H, 4-H and 10-H), 7.41 (d, J = 8.6 Hz, 1H, 11-H); CIMS (NH_3) m/z: 361 ($MH^+ + NH_3$), 344 (MH^+), 328.

*5-Amino-6,7-Dihydro-1,3,9-trimethoxy-5*H-*dibenzo*[a,c]*cycloheptene* ***27***

Oxime **25** (100 mg, 0.3 mmol) was dissolved in absolute *i*PrOH (50 mL) at 90°C under N_2. Sodium (2 g, 86 mmol) was added in one portion and the mixture stirred at 90°C for 1 h. EtOH 95% (30 mL) was poured into the hot solution. The solvent was evaporated and H_2O was added. The aqueous layer was extracted with Et_2O (×3). The organic layer was extracted with HCl (5%). The acidic solution was made basic with NaOH (pellets) and the amine extracted with Et_2O. The organic layer was washed with H_2O and dried (Na_2CO_3). Evaporation gave the amine as a colorless oil, 90 mg (100%): IR ($CHCl_3$): 3700, 3500, 3400 (-NH_2), 1600 (CH-NH_2), 1460 (-CH_2-), 1340, 1290, 1260–1200 (Ph-O-CH_3), 1150, 1055 cm^{-1}; ^1H NMR ($CDCl_3$) δ: 1.9–2.04 (m, 1H, CH_2), 2.3–2.6 (m, 3H, CH_2), 3.69 (s, 3H, CH_3O), 3.71 (s, 3H, CH_3O), 3.76 (s, 3H, CH_3O), 3.81 (m, 1H, *CH*NH_2), 6.45 (d, J = 1.9 Hz, 1H, 2-H), 6.70 (dd, J = 2.6 Hz, 1H, 4-H), 6.76 (m, 1H, 8-H), 6.77 (dd, J = 2.7 and 8.4 Hz, 1H, 10-H), 7.31 (d, J = 8.4 Hz, 1H, 11-H); CIMS (NH_3) m/z: 300 (MH^+), 283 ($MH^+ - NH_3$).

*5-Dimethylamino-6,7-dihydro-1,3,9-trimethoxy-5*H-*dibenzo*[a,c]*cyclohepten* ***28****a*, *5-trimethylamino-6,7-dihydro-1,3,9-trimethoxy-5*H-*didenzo*[a,c]*cycloheptene iodide* ***28****b*, *and 1,3,9-trimethoxy-5*H-*dibenzo*[a,c]*cycloheptene* ***29***

MeI (6 mL) was added to a solution of **27** (190 mg, 0.63 mmol) and *t*BuOK (80 mg, 0.71 mmol) in THF (50 mL). The mixture was stirred at room temperature for 24 h and the insoluble material filtered. The quaternary ammonium salt ***28****b*, which is soluble in THF, was obtained after evaporation of the solution. Ethylene glycol (4 mL), H_2O (4 mL), and KOH (10 g) were added and the mixture was stirred at 190°C for 4 h. After cooling, the solution was diluted with H_2O and extracted with Et_2O; the organic layer was washed with H_2O until neutral and dried (K_2CO_3). Evaporation of the solvent gave an oil (200 mg), which was chromatographed (SiO_2, ethyl acetate – hexanes 1:4, 3:7, 1:1) to give olefin **29** (30 mg) and the dimethylamino compound ***28****a* (70 mg) as an oil. ***28****a* was reacted again with MeI (2 mL) in ethyl acetate at room temperature for 48 h and the mixture directly submitted to Hofmann elimination under the conditions described above to give 20 mg more of olefin **29** (total yield 28%). **29** was crystallized from $MeOH/H_2O$ as white crystals: mp 98–99°C. IR ($CHCl_3$): 3500, 3440, 3000, 2940, 2840 (CH_3), 1600, 1460 (-CH_2-), 1410, 1260, 1240–1200 (Ph-O-CH_3), 1160, 1090, 1060 cm^{-1}; ^1H NMR ($CDCl_3$) δ: 2.84 (ddd, J = 2.0, 5.5, and 12.7 Hz, 1H, 7-Ha), 3.1 (dd, J = 8.1 and 12.7 Hz, 1H, 7-Hb), 3.81 (s, 3H, CH_3O), 3.83 (s, 3H, CH_3O), 3.86 (s, 3H, CH_3O), 6.22 (ddd, J = 5.4, 8.1, and 13 Hz, 1H, 6-H), 6.44 (d, J = 2.6 Hz, 1H, 2-H), 6.47 (d, J = 13.3 Hz, 1H, 5-H), 6.52 (d, J = 2.5 Hz, 1H, 4-H), 6.75 (m, 1H, 8-H), 6.77 (dd, J = 2.8 and 8.6 Hz, 1H, 10-H), 7.56(d, J = 8.3 Hz, 1H, 11-H); CIMS (NH_3) m/z: 283 (MH^+). ***28****a*: IR ($CHCl_3$): 3000, 2940, 2840 (CH_3), 1600 (CH-N), 1450 (-CH_2-), 1420, 1320, 1240–1200 (Ph-O-CH_3), 1150 cm^{-1}; ^1H NMR ($CDCl_3$) δ: 2.04–2.1 (br m, 4H, CH_2), 3.75 (s, 6H, NCH_3), 3.84 (s, 6H, CH_3O), 3.92 (s, 3H, CH_3O), 3.99 (m, 1H, 5-H), 6.49 (d, J = 1.8 Hz, 1H, 2-H); MS (CI/NH_3) m/z: 328 (MH^+), 283 ($MH^+ - NH(CH_3)_2$).

*6,7-Dihydro-1,3,9-trimethoxy-5*H-*dibenzo*[a,c]*cycloheptene* ***5***

From ***26****:* alcohol **26** (80 mg, 0.24 mmol) was dissolved in absolute *i*PrOH (40 mL) and heated at 110°C under N_2, Sodium (3 g, 129 mmol) was added and the mixture stirred at 110°C for 4 h, then at room temperature for 12 h. The unreacted sodium was removed and the reaction was quenched with *i*PrOH/H_2O. Most of the *i*PrOH was evaporated. H_2O (30 mL) was added, and the products were extracted with Et_2O. The organic layer was dried (Na_2CO_3), filtered, and evaporated to give an oil, which was chromatographed (SiO_2, ethyl acetate – hexanes 1:9, 3:7). Compound **5** (10 mg, 15%) was crystallized from petroleum ether as white crystals. Alcohol **30** was obtained as a translucide oil (53 mg, 73%).

Compound ***5****:* mp 109–110°C; IR ($CHCl_3$): 3010, 2940, 2860, 2840 (CH_3), 1610, 1590, 1470 (-CH_2-), 1430, 1350, 1330, 1300, 1260, 1240–1200 (Ph-O-CH_3), 1160, 1090, 1070 cm^{-1}; ^1H NMR ($CDCl_3$) δ: 2.04–2.15 (m, 2H, CH_2), 2.25–2.51 (m, 4H, CH_2), 3.77 (s, 3H, CH_3O), 3.84 (s, 3H, CH_3O), 3.85 (s, 3H, CH_3O), 6.43 (d, J = 2.4 Hz, 1H, 2-H), 6.48 (d, J = 2.4 Hz, 1H, 4-H), 6.79 (d, J = 2.6 Hz, 1H, 8-H), 6.83 (dd, J = 2.8 and 8.4 Hz, 1H, 10-H), 7.41. (d, J = 8.4 Hz, 1H, 11-H); CIMS (NH_3) m/z: 285 (MH^+).

Compound ***30****:* IR ($CHCl_3$): 3620, 3020, 2940, 1610 (Ph), 1460, 1430, 1320, 1300, 1220 (br), 1160, 1050 cm^{-1}; ^1H NMR ($CDCl_3$) δ: 1.72 (br s, 1H, OH), 1.88–2.0 (m, 1H, CH_2), 2.4–2.6 (m, 3H, CH_2), 3.77 (s, 3H, CH_3O), 3.84 (s, 3H, CH_3O), 3.89 (s, 3H, CH_3O), 4.49 (dd, J = 6.3 and 11.1 Hz, 1H, 5-H), 6.52 (d, J = 2.4 Hz, 1H, 2-H), 6.80 (d, J = 2.5 Hz, 1H, 8-H), 6.82 (dd, J = 2.7 and 8.3 Hz, 1H, 10-H), 6.89 (d, J = 2.4 Hz, 1H, 4-H), 7.39 (d, J = 8.2 Hz, 1H, 11-H); CIMS (NH_3) m/z: 301 (MH^+), 2.83 ($MH^+ - H_2O$).

From ***29****:* olefin **29** (21 mg, 0.07 mmol) in acetic acid (4 mL)

was hydrogenated at 1 atm (101.3 kPa) for 3 h in the presence of Pd black (20 mg). After filtration of the catalyst on Celite and evaporation of the filtrate, the residue was dissolved in Et_2O, washed with brine, and dried (Na_2CO_3). Evaporation of the solvent gave an oil, which was crystallized from petroleum ether to give **5** as white crystals (20 mg, 95%).

*Synthesis of DBCH **6** (Scheme 3)*

*2-(2,5-Dimethoxyphenyl)-4,4-dimethyl-2-oxazoline **32***

Oxazoline **32** was prepared according to Meyers' procedure (16). The first acyl chloride intermediate (16), precursor of **32**, was distilled in a Kugelrohr apparatus at 105°C and 0.05 Torr. The oxazoline **32** was purified by distillation in the same manner at 120°C and 0.05 Torr and obtained as a translucent oil (93.4%, 100% pure by GC): IR ($CHCl_3$): 2960 (C-H), 1640 (C=N), 1490, 1460, 1420, 1200 (Ph-O-CH_3), 1140 (C-O) cm^{-1}; ^1H NMR ($CDCl_3$) δ: 1.39 (s, 6H, CH_3), 3.78 (s, 3H, CH_3O), 3.83 (s, 3H, CH_3O), 4.09 (s, 2H, CH_2), 6.88 (d, J = 9.1 Hz, 1H, 3′-H), 6.95 (dd, J = 3 and 9 Hz, 1H, 4′-H), 7.27 (d, J = 3 Hz, 1H, 6′-H); CIMS (NH_3) m/z: 236 (MH^+).

*4,3′,4′-Trimethoxy-2-oxazolinyl-1,1′-biphenyl **33***

Magnesium (4.0 g, 0.17 mmol) and a few crystals of iodine were added to a three-neck, flame-dried, round-bottom flask under argon and heated at 40°C. 4-Bromoveratrole (26 g, 0.12 mol) dissolved in anhydrous THF (150 mL, distilled over $LiAlH_4$) was added dropwise while the temperature was raised to 80°C. The black mixture was stirred at 80°C for 2 h. **32** (7.0 g, 0.03 mol), dissolved in anhydrous THF (100 mL), was added slowly to the Grignard reagent and the mixture stirred under argon at room temperature for 30 h. An aqueous solution of NH_4Cl (100 mL) was added, followed by H_2O (150 mL), and the product was extracted with Et_2O. The organic layer was washed with brine and dried ($MgSO_4$). Evaporation of solvent gave a yellow oil, which was distilled in a Kugelrohr apparatus. Most of the impurities and nonreacted starting material distilled between 80°C and 120°C at 0.05 Torr while the crude product remained in the flask. Oxazoline **33** was purified by chromatography (SiO_2, ethyl acetate – hexanes 3:7, 1:1) to give 8.5 g of yellow oil, which crystallized after drying (84%, 100% pure by GC): mp 73–75°C; IR ($CHCl_3$): 3000, 2970 (C-H), 1640 (C=N), 1600, 1490, 1250–1200 (Ph-O-CH_3), 1040 cm^{-1}; ^1H NMR ($CDCl_3$) δ: 1.31 (s, 6H, CH_3), 3.82 (s, 2H, CH_2), 3.86 (s, 3H, CH_3O), 3.88 (s, 3H, CH_3O), 3.91 (s, 3H, CH_3O), 6.89 (m, 2H, 6-H, 2′-H), 6.92 (dd, J = 2 and 8.1 Hz, 1H, 5-H), 7.01 (dd, J = 2.8 and 8.5 Hz, 1H, 6′-H), 7.22 (d, J = 2.7 Hz, 1H, 3-H), 7.28 (d, J = 8.3 Hz, 1H, 5′-H); CIMS (NH_3) m/z: 342 (MH^+). Anal. calcd. for $C_{20}H_{23}O_4N$: C 70.36, H 6.79, N, 4.10; found: C 70.09, H 6.75, N 3.99.

*3′,4′,4-Trimethoxy-1,1′-biphenyl-2-carbaldehyde **34***

Aldehyde **34** was prepared according to Meyers' procedure (16), purified by column chromatography (SiO_2, ethyl acetate – hexanes 1:4), and obtained as white crystals (30%, 100% pure by GC): mp 98°C; IR ($CHCl_3$): 3000, 2950 (C-H), 1680 (C=O), 1600, 1480, 1460, 1250–1200 (Ph-O-CH_3), 1020, 900 cm^{-1}; ^1H NMR ($CDCl_3$) δ: 3.92 (s, 3H, CH_3O), 3.93 (s, 3H, CH_3O), 3.96 (s, 3H, CH_3O), 6.89 (m, 2H, 2′-H, 5-H), 6.97 (d, J = 8.7 Hz, 1H, 6-H), 7.21 (dd, J = 2.8 and 8.5 Hz, 1H, 6′-H), 7.40 (d, J = 8.6 Hz, 1H, 5′-H), 7.5 (d, J = 2.8 Hz, 1H, 3-H), 10.0 (s, 1H, CHO); CIMS (NH_3) m/z: 273 (MH^+), 255 ($MH^+ - H_2O$). Anal. calcd. for $C_{16}H_{16}O_4$: C 70.58, H 5.92; found: C 70.39, H 5.96.

*Ethyl 3-(3′,4,4′-trimethoxy-1,1′-biphenyl-2-yl)prop-2-enoate **35***

Ester **35** was prepared by published procedure (7*a*) and obtained as white crystals after purification by column chromatography (SiO_2, ethyl acetate – hexanes 1:4) (79%): mp 74–75°C; IR ($CHCl_3$): 3020–2800 (CH_3), 1710 (C=O), 1640 (-CH=CH-), 1600 (Ph), 1500, 1470, 1440, 1340–1140, 1030 cm^{-1}; ^1H NMR ($CDCl_3$) δ: 1.29 (t, J = 7.1 Hz, 3H, CH_3), 3.88 (s, 6H, CH_3O), 3.93 (s, 3H, CH_3O), 4.22 (q, J = 7.1 Hz, 2H, CH_2), 6.37 (d, J = 15.9 Hz, 1H, =CH-CO), 6.81 (d, J = 1.9 Hz, 1H, 2′-H), 6.82 (dd, J = 1.9 and ~8 Hz, 1H, 5-H), 6.93 (d, J = 8 Hz, 1H, 6-H), 6.99 (dd, J = 2.5 and 8.5 Hz, 1H, 6′-H), 7.17 (d, J = 2.6 Hz, 1H, 3-H), 7.31 (d, J = 8.5 Hz, 1H, 5′-H), 7.76 (d, J = 16 Hz, 1H, PhCH=); CIMS (NH_3) m/z: 360 ($MH^+ + NH_3$), 343 (MH^+), 297 ($MH^+ -$ OEt). Anal. calcd. for $C_{20}H_{22}O_5$: C 70.16, H 6.48; found: C 70.11, H 6.53.

*Ethyl 3′,4′,4-trimethoxy-1,1′-biphenyl-2-propionate **36***

Ester **36** was prepared by published procedure (7*a*) (91%): IR ($CHCl_3$): 3010–2820 (CH_3), 1730 (C=O), 1600 (Ph), 1480, 1350–1120 cm^{-1}; ^1H NMR ($CDCl_3$) δ: 1.2 (t, J = 7.1 Hz, 3H, CH_3), 2.43 (t, J ~ 8 Hz, 2H, CH_2CO), 2.92 (t, J ~ 8 Hz, 2H, $PhCH_2$), 3.83 (s, 3H, CH_3O), 3.88 (s, 3H, CH_3O), 3.92 (s, 3H, CH_3O), 4.07 (q, J = 7.2 Hz, 2H, OCH_2), 6.78–6.84 (m, 4H, 2′-H, 6′-H, 3-H, 5-H), 6.9 (d, J = 8 Hz, 1H, 6-H), 7.14 (d, J = 8.2 Hz, 1H, 5′-H); CIMS (NH_3) m/z: 345 (MH^+) 300 ($MH^+ -$ OEt).

*3′,4′,4-Trimethoxy-1,1′-biphenyl-2-propionic acid **37***

Acid **37** was prepared by published procedure (7*a*) and obtained as a white powder (98.3%): mp 148–149°C: IR ($CHCl_3$): 3010, 2940 (CH_3), 1710 (C=O), 1610 (Ph), 1490, 1460, 1290–1190, 1170, 1130 cm^{-1}; ^1H NMR ($CDCl_3$) δ: 2.48 (t, J ~ 8 Hz, 2H, CH_2CO), 2.93 (t, J ~ 8 Hz, 2H, $PhCH_2$), 3.83 (s, 3H, CH_3O), 3.87 (s, 3H, CH_3O), 3.92 (s, 3H, CH_3O), 6.78–6.83 (m, 4H, 2′-H, 6′-H, 3-H, 5-H), 6.9 (d, J = 8.3 Hz, 1H, 6-H), 7.14 (d, J = 8.2 Hz, 1H, 5′-H); CIMS (NH_3) m/z: 334 ($MH^+ + NH_3$), 317 (MH^+), 299 ($MH^+ - H_2O$). Anal. calcd. for $C_{18}H_{20}O_5$: C 68.34, H 6.37; found: C 68.17, H 6.40.

*6,7-Dihydro-2,3,9-trimethoxy-5*H*-dibenzo[*a,c*]cyclohepten-5-one **38***

Acid **37** (510 mg, 1.61 mmol) was suspended in $(CF_3CO)_2O$ (20 mL) at low temperature (ice + NaCl). CF_3COOH (20 mL) was then added dropwise and the solution stirred for 2.5 h at 0°C. The reaction was followed by GC. The solvent was evaporated, the residue taken up in ethyl acetate, washed with $NaHCO_3$ solution, brine, and dried (Na_2SO_4). Evaporation of the solvent gave an oily yellow compound, which was crystallized from ethyl acetate – hexanes and obtained as a white powder (450 mg, 93%): mp 142–143°C; IR ($CHCl_3$): 3020, 2960, 2940 (C-H), 1660 (C=O), 1600 (Ph), 1500, 1460, 1440, 1350, 1290–1120 (Ph-O-CH_3), 1160 cm^{-1}; ^1H NMR ($CDCl_3$) δ: 2.94 (s, 4H, CH_2), 3.86 (s, 3H, CH_3O), 3.96 (s, 3H, CH_3O), 3.98 (s, 3H, CH_3O), 6.82 (d, J = 2.6 Hz, 1H, 8-H), 6.86 (s, 1H, 1-H), 6.89 (dd, J = 2.7 and 8.5 Hz, 1H, 10-H), 7.3 (s, 1H, 4-H), 7.35 (d, J = 8.5 Hz, 1H, 11-H); CIMS (NH_3) m/z: 299 (MH^+). Anal. calcd. for $C_{18}H_{18}O_4$: C 72.47, H 6.08; found: 72.26, H 6.12.

*6,7-Dihydro-2,3,9-trimethoxy-5*H*-dibenzo[*a,c*]cyclohepten-5-ol **39***

Alcohol **39** was prepared by published procedure (7*a*) and obtained as white crystals (92%): dec. >260°C; IR ($CHCl_3$): 3620 (OH), 3020, 2940 (CH_3), 1610 (Ph), 1490, 1460 (-CH_2-), 1290–1180 (Ph-O-CH_3), 1150, 1130, 1050 cm^{-1}; ^1H NMR ($CDCl_3$) δ: 2.48–2.62 (m, 4H, CH_2), 3.85 (s, 3H, CH_3O), 3.92 (s, 3H, CH_3O), 3.96 (s, 3H, CH_3O), 4.60 (dd, J = 6.9 and 9.8 Hz, 1H, 5-H), 6.82 (d, J = 2.6 Hz, 1H, 8-H), 6.87 (s, 1H, 1-H), 6.87 (dd, J = 2.7 and 8.3 Hz, 1H, 10-H), 7.2 (s, 1H, 4-H), 7.27 (d, J = 8.5 Hz, 1H, 11-H); CIMS (NH_3) m/z: 300 (M^+), 283 ($MH^+ - H_2O$).

*2,3,9-Trimethoxy-7*H*-dibenzo[*a,c*]cycloheptene **40***

Cycloheptene **40** was prepared by published procedure (7*a*) and obtained as white crystals after recrystallization from $MeOH/H_2O$ (92%): mp 115–116°C; IR ($CHCl_3$): 3020 (CH_3), 1610 (Ph), 1500, 1470 (-CH_2-), 1290–1180 (Ph-O-CH_3), 1140, 1050 cm^{-1}; ^1H NMR ($CDCl_3$) δ: 2.93 (br s, 2H, CH_2), 3.77 (s, 3H, CH_3O), 3.86 (s, 3H, CH_3O), 3.90 (s, 3H, CH_3O), 6.02 (dt, J = 6.8 and 10 Hz, 1H, 6-H), 6.43 (d, J = 10 Hz, 1H, 5-H), 6.70 (d, J = 2.7 Hz, 1H, 8-H), 6.72 (s, 1H, 1-H), 6.78 (dd, J = 2.7 and 8.6 Hz, 1H, 10-H), 7.04

(s, 1H, 4-H), 7.35 (d, J = 8.5 Hz, 1H, 11-H); MS (CI/NH_3) m/z: 283 (MH^+). Anal. calcd. for $C_{18}H_{18}O_3 \cdot 0.5\ H_2O$: C 74.34, H 6.41; found: C 74.34, H 6.26.

*6,7-Dihydro-2,3,9-trimethoxy-5*H-*dibenzo*[a,c]*cycloheptene* ***6***

Dihydrocycloheptene **6** was prepared by published procedure (*7a*) and crystallized as white crystals from MeOH–H_2O (72%): mp 75–76°C; IR ($CHCl_3$): 3010, 2940, 2860 (CH), 1600 (Ph), 1480, 1460 (-CH_2-), 1240, 1200 (Ph-O-CH_3), 1150, 1130, 1050, 1020 cm^{-1}; ^1H NMR ($CDCl_3$), δ: 2.07 (m, 2H, CH_2), 2.34–2.43 (m, 4H, CH_2), 3.77 (s, 3H, CH_3O), 3.84 (s, 3H, CH_3O), 3.85 (s, 3H, CH_3O), 6.69 (s, 1H, 1-H), 6.73 (d, J = 2.7 Hz, 1H, 8-H), 6.79 (dd, J = 2.7 and 8.3 Hz, 1H, 10-H), 6.81 (s, 1H, 4-H), 7.21 (d, J = 8.3 Hz, 1H, 11-H); CIMS (NH_3) m/z: 285 (MH^+).

Synthesis of DBCH 7 (Scheme 4)

*(S)-5-Acetamido-6,7-dihydro-9,10,11-trimethoxy-5*H-*dibenzo*[a,c]*cyclohepten-3-yl-1-phenyl-1*H-*5-tetrazolyl ether* ***42***

A mixture of *N*-acetylcolchinol (2.0 g, 5.6 mmol), 5-chloro-1-phenyl-1*H*-tetrazole (1.4 g, 7.7 mmol), and K_2CO_3 (1.9 g, 13.7 mmol) in DMF (50 mL, anhydrous, distilled over molecular sieves) was stirred under argon at 80°C for 6 h, then at room temperature for 3 days. H_2O was added and a white solid precipitated that was collected by filtration, dissolved in $CHCl_3$–*i*PrOH, and washed with brine. After drying ($MgSO_4$) and evaporation of solvent, a yellow oil was obtained that was crystallized from Et_2O to give a white powder (2.8 g, 99%): mp 192–193°C $[\alpha]_D^{25}$ −100.2 (c = 0.51, MeOH); IR ($CHCl_3$): 3500–3300 (-CO-NH-R), 3000, 2940 (CH_3), 1670 (C=O), 1600 (Ph), 1530, 1500, 1480, 1450, 1230–1200, 1150, 1100 cm^{-1}; ^1H NMR ($CDCl_3$) δ: 1.53 (s, $COCH_3$), 1.83–1.95 (m, 1H, CH_2), 2.05 (s, $COCH_3$), 2.32–2.55 (m, 3H, CH_2), 3.46 (s, 3H, OCH_3), 3.84 (s, 3H, OCH_3), 3.86 (s, 3H, OCH_3), 4.78–4.87 (m, 1H 82%, 7-H), 5.12 (m, 1H 18%, 7-H), 5.22 (br d, NH), 5.87 (d, J = 7.8 Hz, NH), 6.59 (s, 1H, 4-H), 7.30 (dd, J = 2.7 and 8.5 Hz, 1H, 10-H), 7.46 (d, J = 2.6 Hz, 1H, 8-H), 7.49–7.63 (m, 5H, Ph), 7.84 (d, J = 7.9 Hz, 1H, 11-H); CIMS (NH_3) m/z: 502 (MH^+).

*(S)-7-Acetamido-6,7-dihydro-1,2,3-trimethoxy-7*H-*dibenzo*[a,c]*cycloheptene* ***43***

A mixture of tetrazolyl ether **42** (2.8 g, 5.6 mmol) and 10%Pd/C (3 g) in AcOH (30 mL) was hydrogenated on a Parr apparatus at 50°C under 50 psi (1 psi = 6.89 kPa) of H_2 for 48 h. The catalyst was filtered and washed with AcOH. After evaporation of solvent the residue was dissolved in $CHCl_3$ and washed with NaOH (5%), H_2O, and dried (Na_2SO_4). Evaporation gave a white powder (1.87 g), which was recrystallized from ethyl acetate – hexanes (98%; 100% pure by GC): mp 189°C $[\alpha]_D^{25}$ −33.1 (c = 0.68, MeOH); IR ($CHCl_3$): 3440 (-CO-NH-R), 3000, 2940, (CH_3), 1670 (C=O), 1600, 1500, 1480, 1400, 1250–1200 (Ph-O-CH_3), 1140, 1100 cm^{-1}; ^1H NMR ($CDCl_3$) δ: 1.58 (s, $COCH_3$), 1.67–1.84 (m, 1H, CH_2), 2.06 (s, $COCH_3$), 2.3–2.49 (m, 3H, CH_2), 3.52 (s, CH_3O), 3.58 (s, CH_3O), 3.9 (s, 3H, CH_3O), 3.93 (s, 3H, CH_3O), 4.80–4.89 (m, 1H 78%, 7-H), 5.16–5.18 (m, 1H 22%, 7-H), 5.24 (m, NH), 5.75–5.78 (m, NH), 6.57 (s, 1H, 4-H), 7.25–7.4 (m, 3H, Ph), 7.5 (m, 1H, Ph); CIMS (NH_3) m/z: 359 ($MH^+ + NH_3$), 341 (MH^+).

*(S)-7-Amino-6,7-dihydro-1,2,3-trimethoxy-7*H-*dibenzo*[a,c]*cycloheptene* ***44***

Acetamide **43** (1.8 g, 5.3 mmol) in H_2SO_4 (20%, 100 mL) and MeOH (50 mL) was refluxed for 3 days, when the reaction was found to be complete by GC. After cooling, the solution was made basic with NaOH (5%), then NaOH pellets. The product was extracted with ethyl acetate, washed with H_2O until neutral, and dried (Na_2SO_4). Evaporation of solvent gave an oil, which was chromatographed (SiO_2, $CHCl_3$–MeOH 95:5) to give **44** as white crystals (1.5 g, 95%): mp 95–96°C; $[\alpha]_D^{25}$ −45 (c = 0.61, MeOH); IR ($CHCl_3$): 3000, 2940 (CH_3), 1600 (Ph), 1480, 1450, 1400, 1340, 1250–1180 (Ph-O-CH_3), 1140, 1090, 1000 cm^{-1}; ^1H NMR ($CDCl_3$) δ: 1.68–1.78 (m, 1H, CH_2), 2.28–2.5 (m, 3H, CH_2), 3.64 (s, 3H, CH_3O), 3.83–3.88 (m, 1H, 7-H), 3.92 (s, 6H, CH_3O), 6.60 (s, 1H, 4-H), 7.3–7.42 (m, 2H, 9-H, 10-H), 7.46 (d, J = 7.3 Hz, 1H, 8-H), 7.61 (d, J = 8.2 Hz, 1H, 11-H); CIMS (NH_3) m/z: 300 (MH^+), 283 ($MH^+ - NH_3$).

*1,2,3-Trimethoxy-5*H-*dibenzo*[a,c]*cycloheptene* ***46***

Amine **44** (250 mg, 0.84 mmol) was dissolved in a solution of anhydrous THF (10 mL) and MeI (10 mL). *t*BuOK (200 mg, 1.78 mmol) was added and the mixture stirred for 3 days at room temperature under argon. At this point the amount of ammonium salt **45** formed was very small and the mixture contained mainly the dimethyl amine derivative of **44**. The inorganic material was removed by filtration and the filtrate was evaporated to give a yellow oil that was stirred in MeI (10 mL) for 2 days. The yellow precipitate formed was collected (180 mg) and heated at 190°C for 3 h in a solution of ethylene glycol (4 mL), H_2O (4 mL), and KOH (10 g). After cooling, 20 mL of H_2O was added and the aqueous phase was extracted with Et_2O. The organic layer was washed with H_2O, dried ($MgSO_4$), and evaporated, leaving a yellow oil that was chromatographed (SiO_2, ethyl acetate – hexanes 1:4) to give 100 mg of pure cycloheptene **46**. Recrystallization from MeOH afforded white crystals (42%): mp 124–125°C; IR ($CHCl_3$): 3000, 2940 (CH_3), 1590 (Ph), 1480, 1400, 1330, 1250–1180 (Ph-O-CH_3), 1140, 1110, 1090, 1000 cm^{-1}; ^1H NMR ($CDCl_3$) δ: 2.78 (dd, J = 5.5 and 12.9 Hz, 1H, 5a-H), 3.05 (dd, J = 8.1 and 12.9 Hz, 1H, 5b-H), 3.45 (s, 3H, CH_3O), 3.90 (s, 3H, CH_3O), 3.91 (s, 3H, CH_3O), 6.24 (m, 1H, 6-H), 6.56–6.58 (m, 2H, 4-H, 7-H), 7.26–7.33 (m, 3H, 8-H, 9-H, 10-H), 7.81 (d, J = 7.5 Hz, 1H, 11-H); CIMS (NH_3) m/z: 300 ($MH^+ + NH_3$), 283 (MH^+). Anal. calcd. for $C_{18}H_{18}O_3 \cdot 1/2\ H_2O$: C 74.34, H 6.41; found: C74.70, H 6.28.

*6,7-Dihydro-1,2,3-tetramethoxy-5*H-*dibenzo*[a,c]*cycloheptene 7*

Cycloheptene **46** (70 mg, 0.25 mmol) in AcOH (10 mL) was hydrogenated at room temperature and 50 psi in a Parr hydrogenator for 3 h over Pd black catalyst (150 mg). Pd was removed by filtration through Celite and washed with AcOH. Evaporation of the filtrate gave **7** as an oil, which was purified by column chromatography (SiO_2, ethyl acetate – hexanes 1:4) (50 mg, 71%): IR ($CHCl_3$): 3020, 2940, 2860 (C-H), 1600 (Ph), 1490, 1460, 1410, 1350, 1320, 1280–1180 (Ph-O-CH_3), 1150, 1110, 1090, 1010 cm^{-1}; ^1H NMR ($CDCl_3$) δ: 2.08–2.13 (m, 2H, CH_2), 2.25–2.6 (m, 4H, CH_2), 3.6 (s, 3H, CH_3O), 3.92 (s, 3H, CH_3O), 3.93 (s, 3H, CH_3O), 6.6 (s, 1H, 4-H), 7.24–7.31 (m, 3H, 8-H, 9-H, 10-H), 7.48 (d, J = 7 Hz, 1H, 11-H); CIMS (NH_3) m/z: 302 ($MH^+ + NH_3$), 285 (MH^+).

Synthesis of 5-acetamidodeaminocolchinyl methyl ether (Scheme 5)

*5-Amino-6,7-dihydro-1,2,3,9-tetramethoxy-5*H-*dibenzo*[a,c]*cycloheptene* ***47***

Oxime **25** (250 mg, 0.73 mmol) was dissolved in EtOH (50 mL) and heated at 85–90°C. Raney nickel (3 g) and hydrazine hydrate (10 mL) were added and the mixture stirred at 85–90°C for 1 h. The catalyst was removed by filtration through Celite and the filtrate was evaporated. The residue was dissolved in HCl (5%) and washed with Et_2O. The aqueous layer was then basified with NaOH (30%) and the product extracted with Et_2O, washed with brine, and dried (Na_2CO_3). Evaporation of the solvent gave amine **47** as a colorless oil (230 mg, 95.8%, 98% pure by GC): IR ($CHCl_3$): 3010, 2945, 2845, (CH_3), 1610 (CH-NH_2), 1580, 1490, 1460 (-CH_2-), 1400, 1330, 1300, 1260–1200 (Ph-O-CH_3), 1160, 1135, 1080, 1000 cm^{-1}; ^1H NMR ($CDCl_3$) δ: 1.86 (m, 1H, CH_2), 2.4–2.6 (m, 3H, CH_2), 3.57 (s, 3H, CH_3O), 3.8 (m, 1H, *CH*NH_2), 3.85 (s, 3H, CH_3O), 3.88 (s, 3H, CH_3O), 3.92 (s, 3H, CH_3O), 6.78, (d, J = 2.6 Hz, 1H, 8-H), 6.85 (dd, J = 2.7 and 8.5 Hz, 1H, 10-H), 7.03 (s, 1H, 4-H), 7.38 (d, J = 8.5 Hz, 1H, 11-H); CIMS (NH_3) m/z: 330 (MH^+), 313 ($MH^+ - NH_3$).

*(−)-(aR,5S)-5-Amino-6,7-dihydro-1,2,3,9-tetramethoxy-5*H-*dibenzo*[a,c]*cycloheptene* ***47****a*

Amine **47** (350 mg, 1.06 mmol) dissolved in *i*PrOH (5 mL) was resolved with (+)-dibenzoyl-D-tartaric acid in *i*PrOH (10%, 5 mL) and the salt was recrystallized twice from MeOH. Treatment of this salt with NH_4OH (30%) and extraction with ethyl acetate afforded amine **47***a* (120 mg, 68.7%): $[\alpha]_D^{25}$ −85 (*c* = 0.62, MeOH). Phenylethylurea **48***a* was prepared with *S*-(−)-1-phenylethyl isocyanate in CH_2Cl_2 (22): mp 90–93°C; $[\alpha]_D^{25}$ −55.3 (*c* = 0.93, MeOH); CIMS (NH_3) *m/z*: 477 (MH^+). HPLC purity 100%, retention time 12.6 min (ethyl acetate – hexanes 3:2, 1 mL min^{-1}).

*(+)-(aS,5R)-5-Amino-6,7-dihydro-1,2,3,9-tetramethoxy-5*H-*dibenzo*[a,c]*cycloheptene* ***47****b*

The amine prepared from the mother liquor of the resolution of **47***a* afforded a salt on treatment with (−)-*o,o'*-dibenzoyl-L-tartaric acid in *i*PrOH. After recrystallization from methanol (×2) and basification with NH_4OH (30%), extraction with ethyl acetate gave the oily amine **47***b* (97 mg, 55.6%): $[\alpha]_D^{25}$ +85 (*c* = 0.59, MeOH). Phenylethylurea **48***b* prepared with *S*-(−)-1-phenylethyl isocyanate in CH_2Cl_2 (22): mp 242–243°C; $[\alpha]_D^{25}$ −58.9 (*c* = 0.19, MeOH); CIMS (NH_3) *m/z*: 477 (MH^+). HPLC purity 99.3%, retention time 10.6 min (ethyl acetate – hexanes 3:2, 1 mL min^{-1}).

*5-Acetamido-6,7-dihydro-1,2,3,9-tetramethoxy-5*H-*dibenzo*[a,c]*cyclohepten* ***8****a,b*

Acetic anhydride (0.13 mL, 1.38 mmol) was added, after cooling, to a THF suspension (20 mL) of **47***a,b* (45 mg, 0.14 mmol) and K_2CO_3 (200 mg, 1.4 mmol), and the mixture was stirred at room temperature for 2 h. Saturated $NaHCO_3$ was added and the amide was extracted with Et_2O. The combined extracts were washed with saturated $NaHCO_3$, H_2O, and dried ($MgSO_4$). Evaporation of the solvent gave 66 mg of a colorless oil, which on addition of H_2O gave a white powder.

Compound **8**a: 99%, mp 98–101°C; $[\alpha]_D^{25}$ −68.2 (*c* = 0.505, MeOH); IR ($CHCl_3$): 3440 (-CO-NH-), 3000, 2930, 2840 (CH_3), 1660 (C=O), 1600, 1570 (Ph), 1480, 1450 (-CH_2-), 1400, 1320, 1300, 1240–1200 (Ph-O-CH_3), 1085 cm^{-1}; ^1H NMR ($CDCl_3$) δ: 2.09 (s, 3H, $COCH_3$), 2.3–2.7 (m, 4H, CH_2), 3.56 (s, 3H 45%, CH_3O), 3.59 (s, 3H 55%, CH_3O), 3.84 (s, 3H 43%, CH_3O), 3.87 (s, 3H 57%, CH_3O), 3.89 (s, 3H, CH_3O), 3.90 (s, 3H 50%, CH_3O), 3.92 (s, 3H 50%, CH_3O), 4.64 (m, 1H 46%, 5-H), 5.06 (m, 1H 54%, 5-H), 5.18 (d, *J* = 8.8 Hz, NHCO), 6.16 (br s, NHCO), 6.61 (s, 1H 39%, 4-H), 6.67 (s, 1H 61%, 4-H), 6.76 (d, *J* = 2.6 Hz, 8-H), 6.82–6.94 (m, 1H, 10-H), 6.86 (d, *J* = 2.7 Hz, 8-H), 7.41 (d, *J* = 8.4 Hz, 1H 52%, 11-H), 7.42 (d, *J* = 8.3 Hz, 1H 48%, 11-H); EIMS *m/z*: 371 (M^+), 312 (M^+ − $NHCOCH_3$), 281.

Compound **8**b: 99%, mp 94–95°C; $[\alpha]_D^{25}$ +71.8 (*c* = 0.545, MeOH).

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1. H. G. Capraro and A. Brossi. Alkaloids (Academic Press), **23**, 1 (1984).
2. A. Brossi. J. Med. Chem. **33**, 2315 (1990).
3. A. Muzaffar, A. Brossi, C. M. Lin, and E. Hamel. J. Med. Chem. **33**, 567 (1990).
4. M. Rösner, H. G. Capraro, A. E. Jacobson, L. Atwell, A. Brossi, M. A. Iorio, T. H. Williams, R. H. Sik, and C. F. Chignell. J. Med. Chem. **24**, 257 (1981).
5. M. Cernoch, J. Malinsky, O. Telupilova, and F. Santavy. Arch. Int. Pharmacodyn. Ther. **99**, 141 (1954).
6. P. Kerekes, A. Brossi, J. L. Flippen-Anderson, and C. F. Chignell. Helv. Chim. Acta, **68**, 571 (1985).
7. (*a*) O. Boyé, Y. Itoh, E. Hamel, and A. Brossi. Helv. Chim. Acta, **72**, 1690 (1989); (*b*) Y. Itoh, C. M. Lin, E. Hamel, and A. Brossi. Helv. Chim. Acta, **71**, 1199 (1988).
8. B. Umezawa, O. Hoshino, S. Sawaki, H. Sashida, K. Mori, Y. Hamada, K. Kotera, and Y. Iitaka. Tetrahedron, **40**, 1783 (1984).
9. A. Brossi, H. J. C. Yeh, M. Chrzanowska, J. Wolff, E. Hamel, C. M. Lin, F. Quinn, M. Suffness, and J. V. Silverton. Med. Res. Rev. **8**, 77 (1988).
10. A. Brossi, O. Boyé, A. Muzaffar, H. J. C. Yeh, V. Toome, B. Wegrzynski, and C. George. FEBS Lett. **262**, 5 (1990).
11. V. Prelog and G. Helmchen. Angew. Chem. Int. Ed. Engl. **21**, 567 (1982).
12. H. House. Modern synthetic reactions. 2nd ed. W. A. Benjamin, Menlo Park, Calif. 1972. p. 201.
13. H. Zimmermann. Tetrahedron, **16**, 169 (1961).
14. A. I. Meyers, R. Gabel, and E. D. Michelich. J. Org. Chem. **43**, 1372 (1978).
15. A. I. Meyers, J. R. Flisak, and J. R. Aitken. J. Am. Chem. Soc. **109**, 5446 (1987).
16. A. I. Meyers and M. E. Flanagan. Org. Synth. **69**, 248 (1990).
17. J. W. Cook and J. D. Loudon. Alkaloids (Academic Press), **2**, 278 (1952); A. Windaus. Liebigs. Ann. Chem. **439**, 59 (1924).
18. M. Shamma. The isoquinoline alkaloids. Organic Chemistry Monographs. Vol. 25. Academic Press, San Diego, Calif. 1972. p. 208.
19. K. C. Rice and A. Brossi. Synth. Commun. **8**, 391 (1978).
20. W. J. Musliner and J. W. Gates. J. Am. Chem. Soc. **88**, 4271 (1966).
21. A. Brossi, M. F. Rahman, K. C. Rice, M. Gerecke, R. Borner, J. P. O'Brien, and S. Teitel. Heterocycles, **7**, 277 (1977).
22. B. DeCosta, C. George, R. B. Rothman, A. E. Jacobson, and K. C. Rice. FEBS Lett. **223**, 335 (1987).
23. L. M. Jackman and S. Sternhell. Applications of NMR spectroscopy in organic chemistry. 2nd ed. Pergamon Press, New York. 1969. p. 281.
24. C. A. G. Haasnoot, F. A. A. M. de Leeuw, and C. Altona. Tetrahedron, **36**, 2783 (1980).
25. J. K. Batra, G. J. Kang, L. Jurd, and E. Hamel. Biochem. Pharmacol. **37**, 2595 (1988).